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The Western Journal of Medicine

VOLUME 140 • NUMBER 1

JANUARY 1984

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*Analogous to cephalothin, the primary antibiotic disc used in testing
†Numbers under percentages refer to the projected number of isolates tested
Source: The Bacteriologic Report, BAC-DATA Medical Information Systems, Inc., Winter Series 1981-82.

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Bactrim is indicated for the treatment of recurrent urinary tract infections due to susceptible strains of *Escherichia coli*, *Klebsiella-Enterobacter* and the *Proteus* species. However, it is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single antimicrobial agent rather than the combination.

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in recurrent urinary tract infections

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More positive clinical results

Comparative studies of BACTRIM and other agents used in urinary tract infections

Reference	Number of Patients	Therapy	Dosage	Type of Study	Results
Cooper, Brumfitt, Hamilton-Miller[1] (1980)	41 43	Bactrim cephradine	160 mg trimethoprim & 800 mg sulfamethoxazole *t.i.d.* 500 mg *q.i.d.*	Randomized comparison	Cure rate with Bactrim = 85.4%; with cephradine = 69.8% after two weeks
Gower, Tasker[2] (1976)	46 47	Bactrim cephalexin	160 mg trimethoprim & 800 mg sulfamethoxazole *b.i.d.* 1000 mg *b.i.d.*	DB	Cure rate with Bactrim = 96%; with cephalexin = 68% two weeks after therapy
Cosgrove, Morrow[3] (1974)	15 15	Bactrim ampicillin	160 mg trimethoprim & 800 mg sulfamethoxazole *b.i.d.* 500 mg *q.i.d.*	DB	Bactrim proved more effective in uncomplicated chronic UTI
Iravani *et al*[4] (1981)	64 71	Bactrim nalidixic acid	160 mg trimethoprim & 800 mg sulfamethoxazole *b.i.d.* 1 Gm *q.i.d.*	Randomized comparison	Cure rate with Bactrim = 93%; with nalidixic acid = 90% one week after therapy
Schaeffer, Flynn, Jones[5] (1981)	20 20	Bactrim cinoxacin	160 mg trimethoprim & 800 mg sulfamethoxazole *b.i.d.* 500 mg *b.i.d.*	Randomized comparison	Both agents equally effective

References: 1. Cooper J, Brumfitt W, Hamilton-Miller JMT: *J Antimicrob Chemother* 6:231-239, 1980. **2.** Gower PE, Tasker RW: *Br Med J* 1:684-686, Mar 20, 1976. **3.** Cosgrove MD, Morrow JW: *J Urol* 111:670-672, May 1974. **4.** Iravani A *et al*: *Antimicrob Agents Chemother* 19:598-604, Apr 1981. **5.** Schaeffer AJ, Flynn S, Jones J: *J Urol* 125:825-827, Jun 1981. **6.** Kramer MJ, Mauriz YR, Robertson TL, Timmes MD: Morphological studies on the effect of subinhibitory and inhibitory doses of a sulfamethoxazole-trimethoprim combination on *Escherichia coli*. Presented at the 12th International Congress of Chemotherapy, Florence, Italy, July 19-24, 1981.

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For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: *Not recommended for infants less than two months of age.*

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

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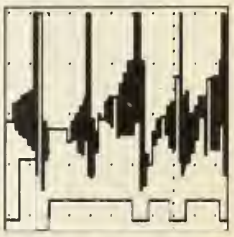

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From the Department of Surgery, University of Washington School of Medicine, Seattle.

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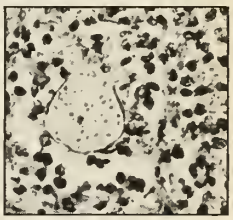
60 **Palpable Leg Purpura and Renal Failure in a 23-Year-Old Man**
Moderator: FRANCISCO P. QUISMORIO, JR, MD
Discussants: RICHARD H. BLAU, MD; MOHAMMAD AKMAL, MD, and MICHAEL KOSS, MD
Edited proceedings of a Rheumatology Grand Rounds Conference at the LAC-USC Medical Center, Los Angeles.



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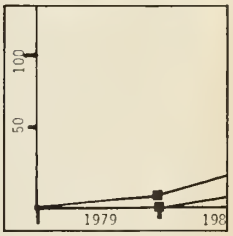
66 **The Acquired Immune Deficiency Syndrome (AIDS)—A Multidisciplinary Enigma**
Discussants: JOHN E. CONTE, JR, MD; ARTHUR J. AMMANN, MD; SELMA K. DRITZ, MD; PAUL VOLBERDING, MD; STEPHEN M. FOLLANSBEE, MD; HERBERT A. PERKINS, MD, and JAY A. LEVY, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.



EPITOMES OF PROGRESS

Chest Diseases—Important Advances in Clinical Medicine
Items of progress in chest diseases. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

82 **Strange Causes of Asthma**
DONALD P. TASKIN, MD

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CORGARD®
(nadolol tablets)
ONCE A DAY FOR HYPERTENSION

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.
PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.
OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.
DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.
HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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Less chance of depression, insomnia and nightmares than propranolol

Because hydrophilic (water-soluble) Corgard® (nadolol tablets) does not readily cross the blood-brain barrier, CNS side effects should occur less frequently than with highly lipophilic propranolol.*

The most commonly reported CNS side effects of Corgard, dizziness and fatigue, have each been reported in approximately 2 of 100 patients receiving Corgard.*

Once-a-day Corgard is as effective as propranolol, qid, in both hypertension and angina pectoris.[1]

Once-a-day

CORGARD®
(nadolol tablets)

*For a full discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary.

1. Data on file: Squibb Institute for Medical Research.

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EQUALLY EFFECTIVE AND MORE PRACTICAL FOR HYPERTENSION

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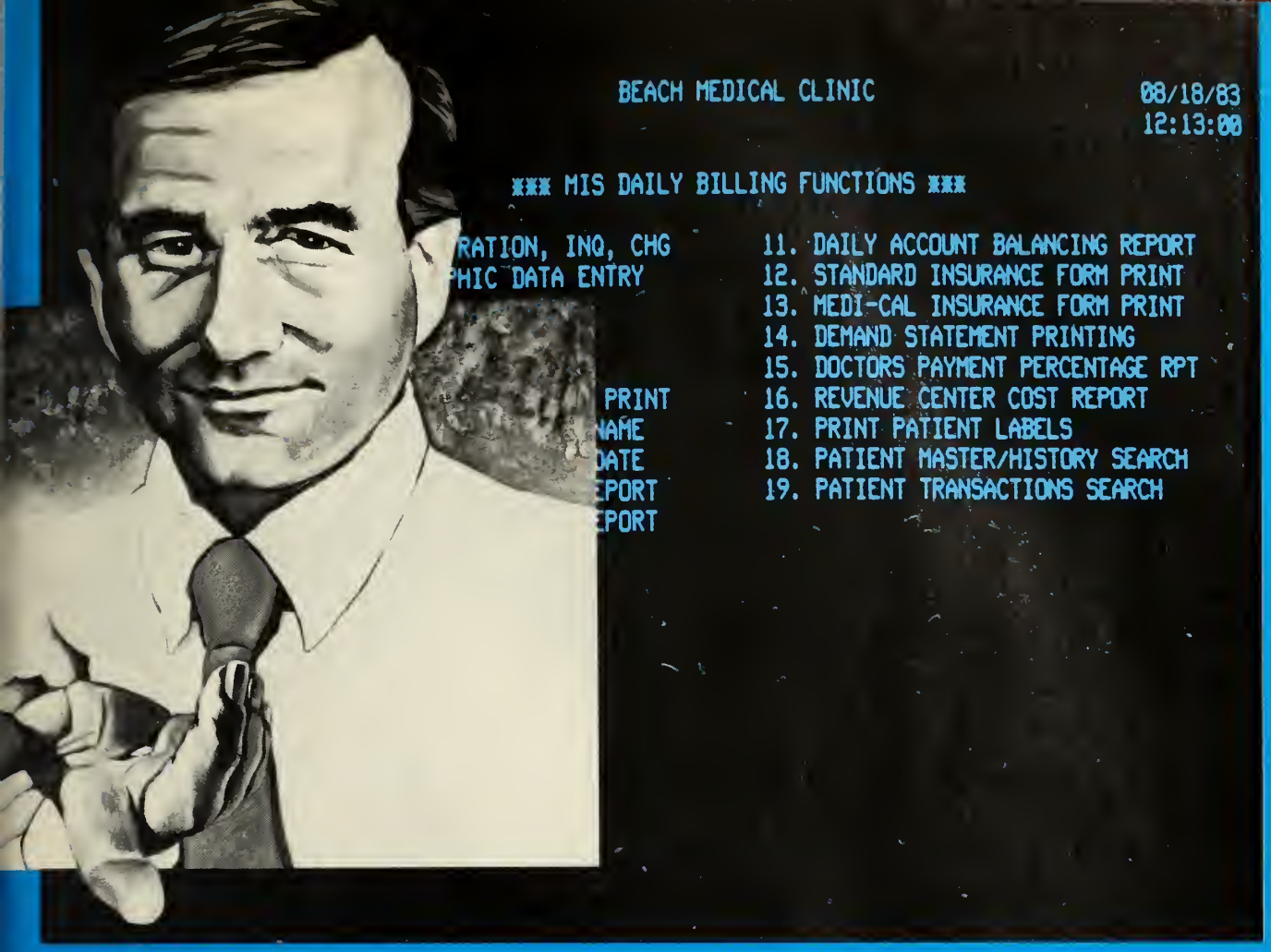

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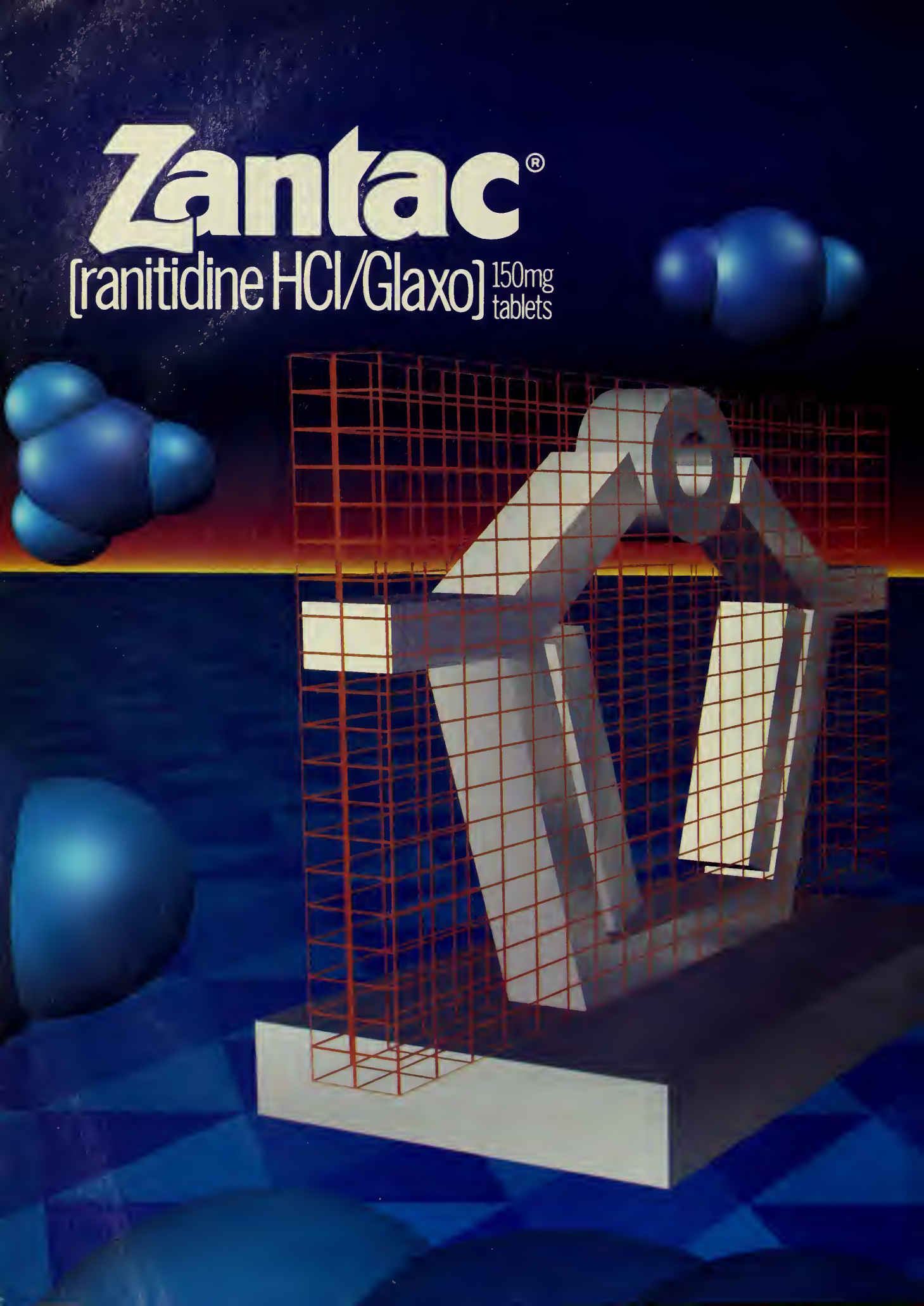
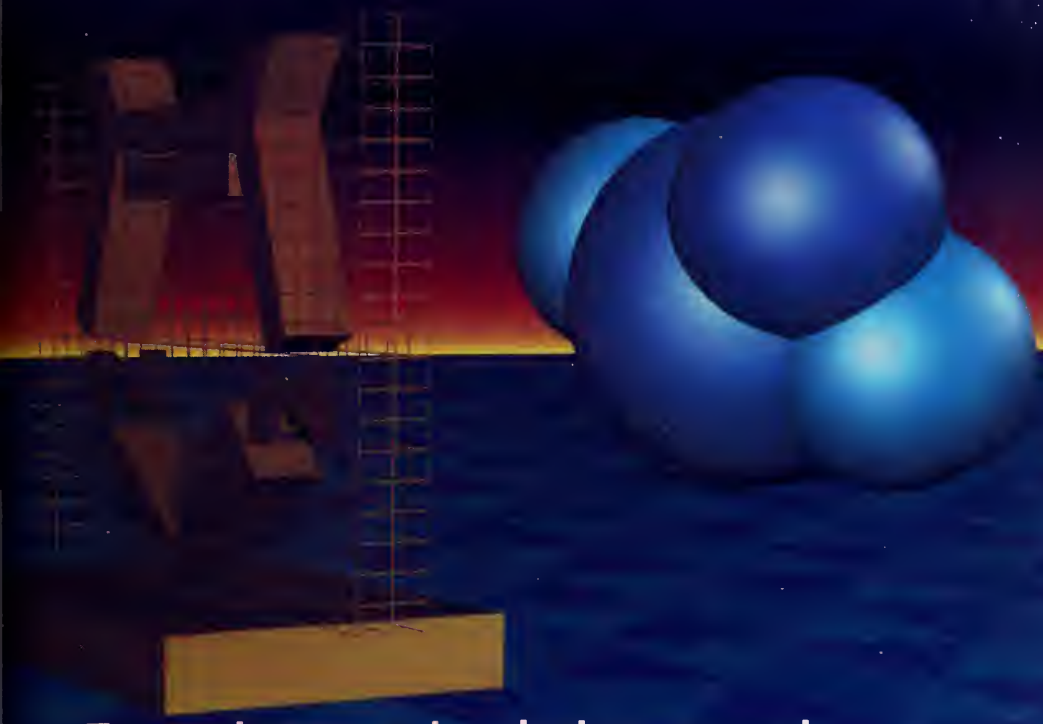
[ranitidine HCl/Glaxo] 150mg tablets



Glaxo ROCHE

Unsurpassed activity in gastric acid inhibition: for active duodenal ulcer and pathological hypersecretory conditions*



Zantac is a new chemical compound

- ☐ Not a histamine-related imidazole—a furan compound.

Zantac offers important patient benefits

- ☐ Single-dose action for up to 12 hours—b.i.d. administration. Four weeks of therapy for most patients with active duodenal ulcer.
- ☐ No interaction with warfarin, theophylline and diazepam.
- ☐ Effective and well tolerated even in pathological hypersecretory conditions.
- ☐ For adverse reactions see complete prescribing information.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers.

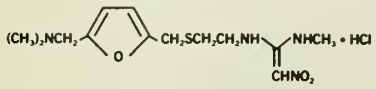
Please see following page for complete prescribing information.

Unsurpassed activity in gastric acid inhibition

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTIDN: The active ingredient in ZANTAC* Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACDLDGY: ZANTAC* (rantidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. Effects on acid secretion:

ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC* on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. Effects on other gastrointestinal secretions:

Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.

Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. Dther pharmacological actions:

a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. Pharmacokinetics:

ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Duodenal Ulcer

In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC*-treated patients as shown below:

	ZANTAC* +		Placebo +	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid	
	Ulcer Healed	Ulcer Not Healed
ZANTAC*	0.06	0.71
Placebo	0.71	1.43

Ouring the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)

ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIDNS AND USAGE:

ZANTAC* (ranitidine hydrochloride) is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.

2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CDNTRAINDICATIDNS: There are no known contraindications to the use of ZANTAC* (ranitidine hydrochloride).

PRECAUTIDNS:

General

1. Symptomatic response to ZANTAC* therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Oosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests

False positive tests for urine protein with Multistix* may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction

Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility

There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and fats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. Coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC* (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIDNS

Headache has been found to be more frequent in ZANTAC*-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Oecreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

DVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC* in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DDSAGE AND ADMINISTRATION:

Duodenal Ulcer

The current recommended adult oral dosage of ZANTAC* for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

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Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Issued Sept. 1983

Glaxo

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

COMPUTED TOMOGRAPHY OF THE PANCREAS, Volume 1 in the CONTEMPORARY ISSUES IN COMPUTED TOMOGRAPHY SERIES. Edited by Stanley S. Siegelman, MD, Professor of Radiology, The Johns Hopkins University School of Medicine, and Director of Diagnostic Radiology, The Johns Hopkins Hospital, Baltimore. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 252 pages, $39.00.

COMPUTED TOMOGRAPHY OF THE SPINE—Volume 2 in the CONTEMPORARY ISSUES IN COMPUTED TOMOGRAPHY SERIES—Edited by Victor M. Haughton, MD, Professor of Radiology, The Medical College of Wisconsin, Milwaukee. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 221 pages, $35.00.

CURRENT CONCEPTS IN CLINICAL CARDIOLOGY: 10th Conference on Cardiovascular Disease in Snowmass-at-Aspen, Colo, January 1979—Volume 27 of ADVANCES IN CARDIOLOGY—Editor, John H. K. Vogel, Santa Barbara, Calif. S. Karger AG, Medical and Scientific Publishers, Arnold-Bocklin-Strasse 25, CH-4011 Basel, Switzerland, 1980. 360 pages, $118.75.

THE FIRST MONTH OF LIFE—A PARENT'S GUIDE TO CARE OF THE NEWBORN—2nd Edition—Glenn R. Stoutt, Jr, MD, Associate Clinical Professor of Pediatrics, University of Louisville School of Medicine, Louisville, Ky. Medical Economics Books, Oradell, NJ 07649, 1983. 171 pages, $9.95.

HANDBOOK OF INTENSIVE CARE—Edited by W. H. Bain, MD, FRCS (Edin), FRCS(Glas), Titular Professor of Cardiac Surgery, University of Glasgow, and Consultant Cardiac Surgeon, Western Infirmary, Royal Infirmary and Stobhill Hospital, and K. M. Taylor, MD, FRCS, FSA(Scot), Senior Lecturer in Cardiac Surgery, University of Glasgow, and Consultant Cardiac Surgeon, Western Infirmary and Royal Infirmary, Glasgow, Scotland. John Wright • PSG Inc., Littleton, MA 01460, 1983. 559 pages, $56.00.

HANDBOOK OF PEDIATRICS—14th Edition—Henry K. Silver, MD, Professor of Pediatrics, and C. Henry Kempe, MD, Professor of Pediatrics and Microbiology, University of Colorado School of Medicine, Denver, and Henry B. Bruyn, MD, Clinical Professor of Medicine and Pediatrics, University of California, San Francisco, School of Medicine, and Consultant in Child Health, City and County of San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 852 pages, $13.00 (softbound).

HOW TO WRITE AND PUBLISH A SCIENTIFIC PAPER—Second Edition—Robert A. Day. ISI Press, 3501 Market St., University City Science Center, Philadelphia, PA 19104, 1983. 174 pages, $17.95 (hardbound), $11.95 (softbound).

HUMAN SEXUALITY AND ITS PROBLEMS—John Bancroft, MD, MRCP, FRCPsych, MRC Reproductive Biology Unit, Edinburgh. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 438 pages, $24.95 (softbound).

INTERDISCIPLINARY TOPICS IN GERONTOLOGY—Volume 17—SOCIAL GERONTOLOGY—Edited by Michael B. Kleiman, Tampa, Florida. S. Karger AG, P.O. Box CH-4009, Sasel, Switzerland, 1983. 202 pages, $58.75 (softbound).

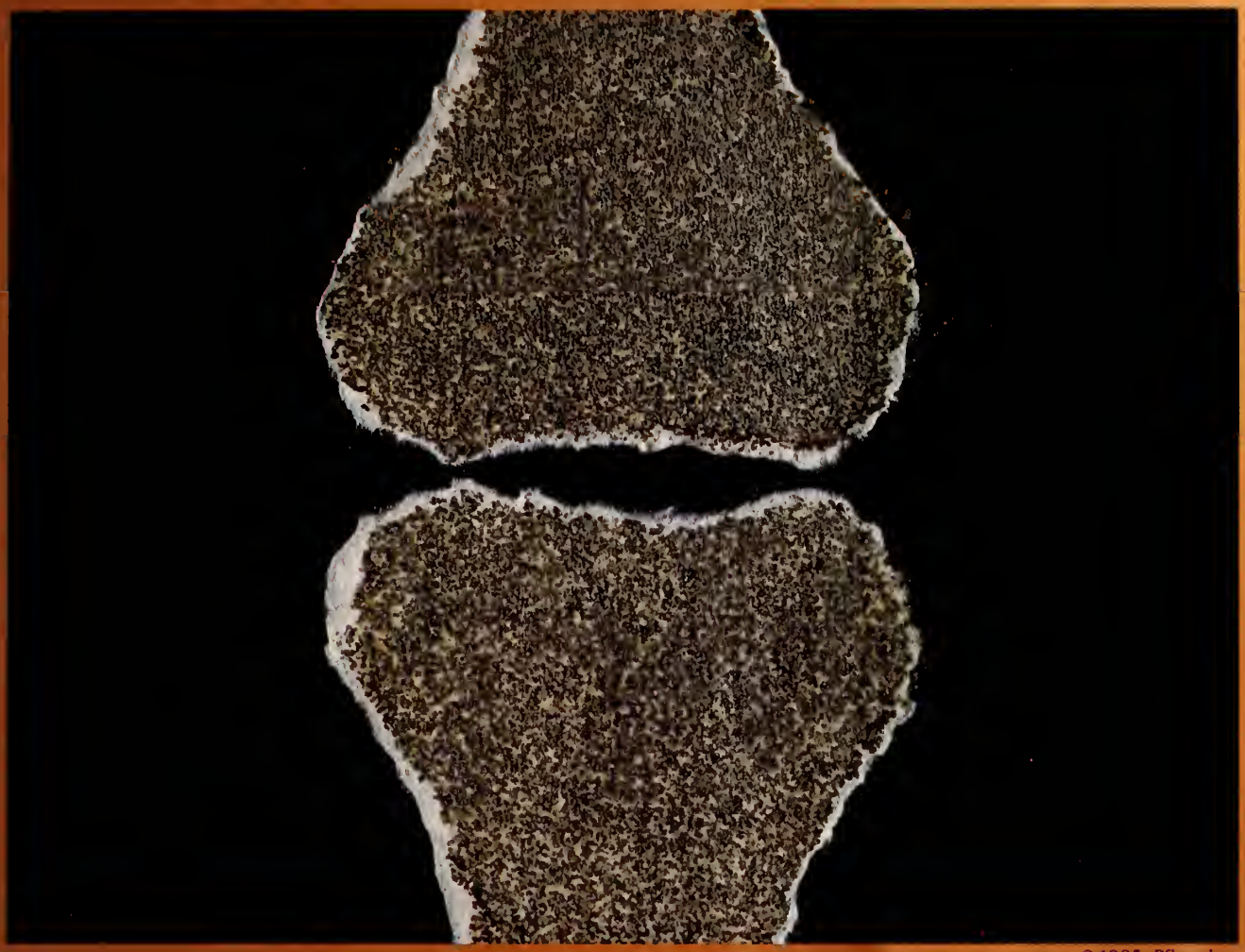
THE JOY OF YOGA—Rosalind Widdowson. Doubleday & Company, Inc., 245 Park Avenue, New York, NY 10167, 1983. 93 pages, $9.95 (softbound).

LEGAL ASPECTS OF MEDICAL PRACTICE—Third Edition—Bernard Knight, MD (Wales), FRC Path, DMJ of Gray's Inn, Barrister-at-Law, Professor of Forensic Pathology, Welsh National School of Medicine, University of Wales, Cardiff; Honorary Consultant Pathologist, South Glamorgan Health Authority (Teaching); Home Office Pathologist. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 302 pages, $17.25.

MALARIA—British Medical Bulletin, Volume 38, No. 2—Edited by S. Cohen, MD, PhD, FRS. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 103 pages, $19.50.

MANAGEMENT OF COMMON PROBLEMS IN OBSTETRICS AND GYNECOLOGY—Daniel R. Mishell Jr, MD, Professor and Chairman, and Paul F. Brenner, MD, Associate Professor, Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles. Medical Economics Books, Oradell, NJ 07649, 1983. 531 pages, $27.50.

MANAGING MEDICINE—Major Contributor: Lawrence L. Weed, MD, Professor of Medicine, University of Vermont; Editor: Jay Stuart Wakefield. MCSA (Medical Communications and Services Association), 10223 N.E. 58th, Kirkland, WA 98033, 1983. Approx. 200 pages, $20.00 (softbound).



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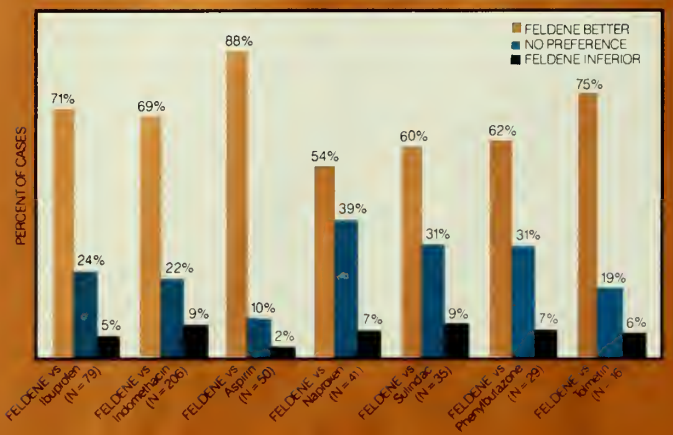

(Adapted from Dessain P. in Postgrad Med J, Apr. 1982.)

Investigators' global comparisons of Feldene and previous medications in multicenter open trials by 156 physicians in 749 osteoarthritis patients who had been on previous drug therapy. The above chart includes only those drugs available in the U.S. Average FELDENE dose was 20 mg/day.

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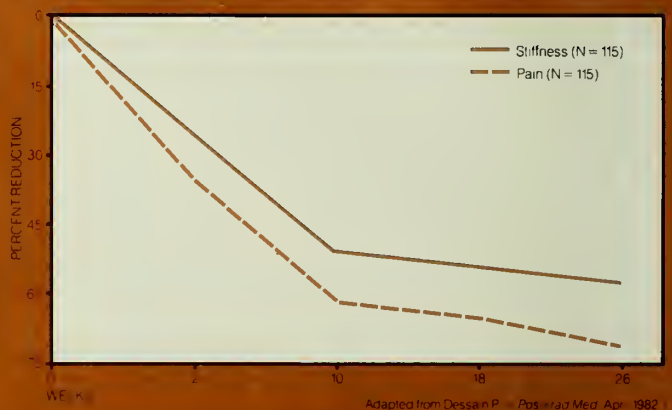
Patients with osteoarthritis evaluated over 6 months on Feldene (mean dose of 20 mg/day) therapy showed dramatic reduction in pain and stiffness.



Adapted from Dessain P. in Postgrad Med, Apr. 1982.

Multicenter long-term follow-up of 154 patients who had shown adequate response to piroxicam in short-term trials. 115 patients for whom complete data were available at every assessment visit through 26 weeks.

Reference

1. Dessain P. [illegible] and [illegible] of piroxicam in general practice: A multicenter study of [illegible] in Postgrad Med J, [illegible] Apr. 1982.

Brief Summary

FELDENE® (piroxicam) Capsules — *For Oral Use*

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation, and G.I. bleeding—sometimes severe, and in rare instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS). In controlled clinical trials, incidence of peptic ulceration with the maximum recommended FELDENE capsule dose of 20 mg per day was 0.8%. The use of doses higher than the recommended dose is associated with an increase in the incidence of gastrointestinal irritation and ulcers.

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

As with other drugs that inhibit prostaglandin biosynthetase, reversible elevations of BUN have been reported in clinical studies with FELDENE. The effect is thought to derive from inhibition of renal prostaglandin synthesis resulting in a change in medullary and deep cortical blood flow with an attendant effect on renal function. Because of the extensive renal excretion of piroxicam, patients with impaired renal function should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when FELDENE is administered.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Less than 1% of patients receiving FELDENE have shown reversible elevation of one or more liver function parameters. While concurrent aspirin may have been involved in some of these changes, a relationship to FELDENE could not be excluded. Studies in patients with impaired liver function have not been done.

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed. Therefore, these values should be determined if signs or symptoms of anemia occur.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with compromised cardiac function, hypertension or other conditions predisposing to fluid retention.

DRUG INTERACTIONS: FELDENE is highly protein bound and, therefore, might be expected to displace other protein-bound drugs. Although *in vitro* studies have shown this not to occur with dicoumarol, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE (piroxicam) is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: The incidence of adverse reactions to piroxicam is based on clinical trials involving approximately 2300 patients, about 400 of whom were treated for more than one year and 170 for more than two years. About 30% of all patients receiving daily doses of 20 mg of FELDENE experienced side effects. Gastrointestinal symptoms were the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Other than the gastrointestinal symptoms, edema, dizziness, headache, changes in hematological parameters and rash have been reported in a small percentage of patients. Routine ophthalmoscopy and slit lamp examinations have revealed no evidence of ocular changes in 205 patients followed from 3 to 24 months while on therapy.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, and indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), leukopenia, eosinophilia.

Urogenital: BUN elevations (see PRECAUTIONS).

Central Nervous System: dizziness, somnolence, vertigo.

Special Senses: tinnitus.

Body as a Whole: headache, malaise.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

Dermatological: pruritus, rash.

*Reactions occurring in 3% to 6% of patients treated with FELDENE.

Incidence Less Than 1%: (Causal Relationship Probable)

There is probably a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration, and dry mouth.

Hematological: thrombocytopenia.

Dermatological: sweating, erythema, bruising, desquamation, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, photosensitivity, allergic skin reactions.

Special Senses: swollen eyes, blurred vision, eye irritations.

Body as a Whole: pain (colic).

Cardiovascular/Respiratory: hypertension (see PRECAUTIONS).

Urogenital: hematuria.

Metabolic: hypoglycemia, weight increase, weight decrease.

Central Nervous System: depression, insomnia, nervousness.

Incidence Less Than 1%: Causal Relationship Unknown.

Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Cardiovascular/Respiratory: palpitations, dyspnea.

Central Nervous System: akathisia.

Urogenital: dysuria.

Hematological: aplastic anemia.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of some adverse reactions and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply.

ADMINISTRATION AND DOSAGE: **Rheumatoid Arthritis, Osteoarthritis:** It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided. Because of the long half-life of FELDENE, steady-state blood levels are not reached for 7–12 days. Therefore, although the therapeutic effects of FELDENE are evident early, treatment therefore is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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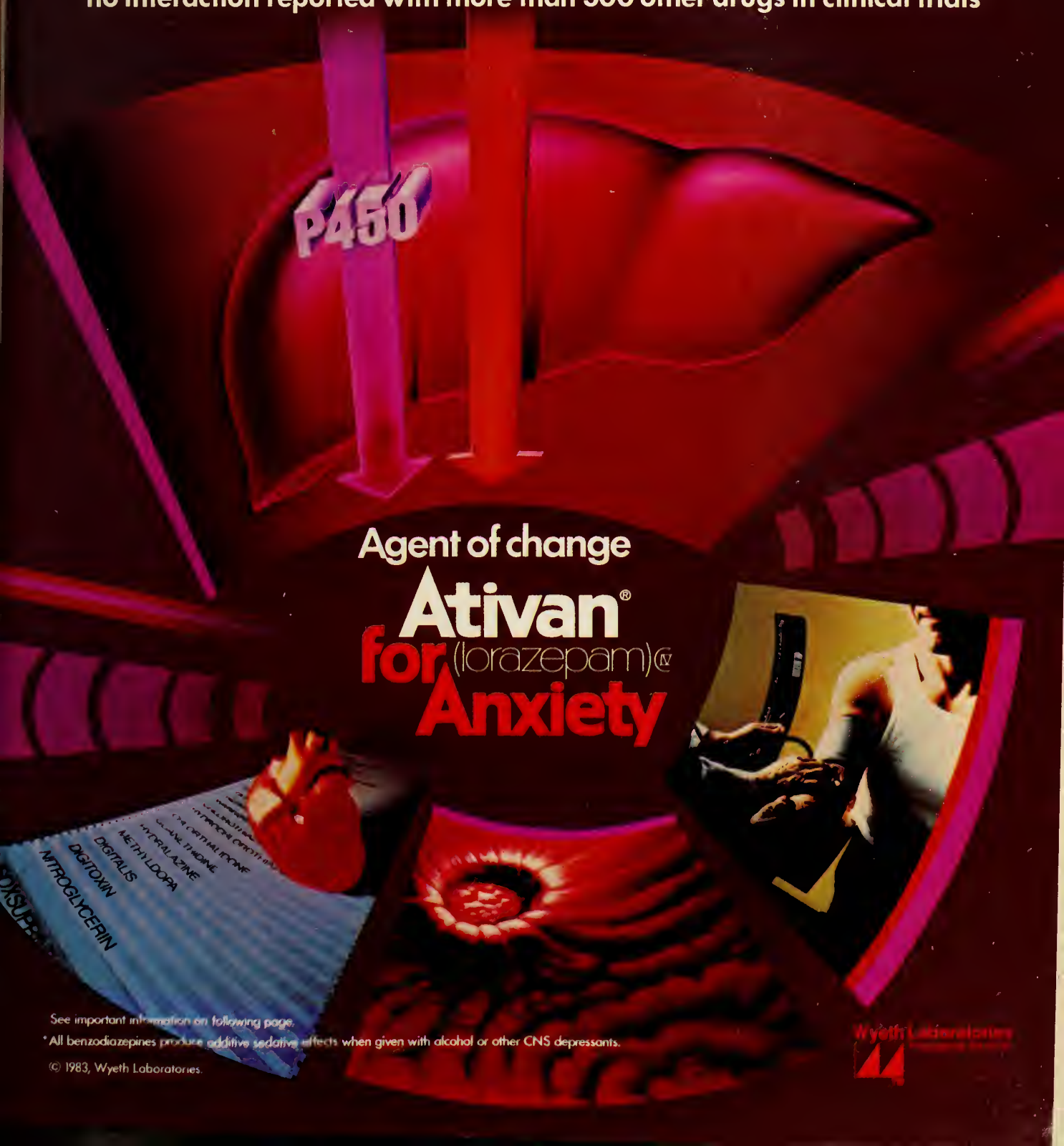

See important information on following page.

*All benzodiazepines produce additive sedative effects when given with alcohol or other CNS depressants.

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NEW TABLET DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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Continuing Medical Education

California, Hawaii, Nevada

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CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

February 29-March 3—**7th Annual Course: Immunology and Clinical Practice of Allergy.** UCSD. Wednesday-Saturday. 20 hrs.

March 1-3—**8th Annual Course: Immunology and the Clinical Practice of Allergy.** American Academy of Allergy and Immunology and UCSD at San Diego Hilton Hotel, Mission Bay, San Diego. Thursday-Saturday. Contact: UCSD.

ANESTHESIOLOGY

January 27-29—**22nd Annual Clinical Conference in Pediatric Anesthesiology.** Childrens Hospital of Los Angeles at Los Angeles Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Wayne Herbert, MD, Program Director, 4650 Sunset Blvd., Los Angeles 90054. (213) 669-2262.

February 11-18—**4th Conference on Intensive Care Medicine.** Ohio State University, Department of Anesthesiology at Royal Hawaiian Hotel, Waikiki, HI and Hilton Hotel, Kona, HI. One week. 20 hrs. Contact: The Ohio State University Hospital, Dept. of Anesthesiology, 410 W. 10th Ave., Columbus, Ohio 43210. (614) 421-8487.

February 18-19—**American Society of Anesthesiologists Regional Refresher Course** at San Francisco Hilton Hotel. Saturday-Sunday. Contact: ASA, 515 Busse Hwy, Park Ridge, IL 60068. (312) 825-5586.

February 18-24—**12th Obstetric Anesthesia Conference.** Ohio State University Hospital, Dept. of Anesthesiology at Sheraton Waikiki Hotel, Waikiki, HI. One week. 20 hrs. Contact: The Ohio State University Hospital, Dept. of Anesthesiology, 410 W. 10th Ave., Columbus, Ohio 43210. (614) 421-8487.

April 9-13—**Critical Care Medicine 10th Hawaiian Seminar.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Monday-Friday. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

CANCER

February 1—**Cancer in the 80s—Breakthroughs in Diagnosis and Treatment.** The Hospital of the Good Samaritan at The Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, Coordinator of Symposia, 616 S. Witmer St., Los Angeles 90017. (213) 977-2352.

February 15-17—**Clinical Laboratory Molecular Analyses: New Strategies in Autoimmunity, Cancer, and Virology.** Scripps Clinic and Research Foundation and Mayo Clinic at Vacation Village, San Diego. Wednesday-Friday. 21 hrs. $290. Contact: Dianne Tisue, Dept. of Academic Affairs, 400S, Scripps Clinic and Research Fndn, 10666 N. Torrey Rd., La Jolla 93037.

February 24-25—**Intra-Arterial and Intracavitary Chemotherapy 1984.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Saturday. 14 hrs. $250.

March 1-3—**UCLA Winter Oncology Conference.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Thursday-Saturday. 18.5 hrs. $360.

CARDIOLOGY

January 20-22—**Doppler Echocardiography.** Institute for Medical Studies at MGM Grand Hotel, Las Vegas. Friday-Sunday. 13.5 hrs. $350. Contact: Kim Stroich, IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

January 23-27—**8th Annual Hawaii Echocardiography Conference.** Honolulu Medical Group Research and Education

(Continued on Page 25)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321. ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine. 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

JUST ONCE-DAILY FOR INITIAL THERAPY IN HYPERTENSION

Unique, once-daily formulation providing comprehensive cardiovascular protection

INDERAL LA offers the antihypertensive and cardiovascular benefits of INDERAL–with the additional advantage of convenient, single daily dosage. With a unique controlled-release formulation, INDERAL LA (propranolol HCl) provides sustained plasma levels and consistent, 24-hour beta blockade.

Smooth 24-hour blood pressure control

In controlled clinical studies, INDERAL LA effectively maintained systolic and diastolic blood pressure reductions with single daily dosing.

Avoids the potassium loss associated with diuretics

INDERAL LA controls blood pressure without the problem of hypokalemia often associated with long-term diuretic therapy. Like conventional INDERAL, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

THE ONE™ TO COUNT ON

Start with 80 mg once daily...

Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. When converting patients from other beta blockers, including INDERAL tablets, start with the nearest milligram equivalent of INDERAL LA once daily and evaluate clinical results to determine if dosage adjustment is necessary. For arrhythmias, use conventional INDERAL (propranolol HCl) tablets.

The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

Please see next page for brief summary of prescribing information.

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INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

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The one to count on for HYPERTENSION, ANGINA and prevention of MIGRAINE.

ONCE-DAILY

INDERAL® LA

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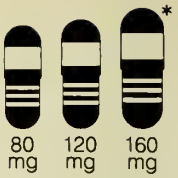

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR)*
INDERAL® LA BRAND OF propranolol hydrochloride
(Long Acting Capsules)
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta-blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block; hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized*. The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized*. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized*. The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

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New York, N.Y. 10017

(Continued from Page 21)

Foundation at Kahala Hilton Hotel, Honolulu. Monday-Friday. Contact: Yvonne Brewer, MPH, Education Director, HMGREF, 550 S. Beretania St., Honolulu, HI 96813. (808) 517-2211, ext. 751.

January 28—**The Grand Design.** See Surgery, January 28.

January 30-31—**Advanced Cardiac Life Support.** See Emergency Medicine, January 30-31.

January 30-February 3—**Current Concepts in Cardiology.** American College of Cardiology and Coronado Hospital at Hotel Del Coronado, Coronado. Monday-Friday. Contact: Registration Secretary, Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

February 10-12—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Sheraton Hotel, Santa Barbara. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

February 11—**Laser Ablation of Coronary Atheroma.** See Surgery, February 11.

February 14-17—**2nd Annual Hawaii Cardiology Update.** Institute for Medical Studies and Straub Clinic at Hilton Hawaiian Village, Honolulu. Tuesday-Friday. 13.5 hrs. $350. Contact: Kim Stroich, IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

February 15-18—**Cardiopulmonary Management of the Critically Ill Patient.** American College of Chest Physicians at Sheraton Palace Hotel, San Francisco. Wednesday-Saturday. Contact: ACCP, Div. of Ed., 911 Busse Hwy, Park Ridge, IL 60068.

February 16-18—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology and Orange Coast Heart Institute, Hoag Memorial Hospital Presby. at Newport Beach Marriott Hotel and Tennis Club, Newport Beach. Thursday-Saturday. Contact: Registration Secretary, Extramural Programs Department, ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

February 23-25—**Duplex Scanning.** Scripps Clinic and the Institute for Medical Studies at San Diego. Thursday-Saturday. 15 hrs. Contact: Kim Stroich, IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

March 2-4—**Cardiovascular Disease: Non-Invasive Diagnostic Methods and Cardiac Rehabilitation.** International Medical Education Corporation at Islandia Hyatt, San Diego. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

March 4-7—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday. $15 hrs. $225.

March 9-11—**Pathophysiology and Techniques of Cardiopulmonary Bypass IV.** See Surgery, March 9-11.

March 16-18—**Advanced Cardiovascular Diagnostic, Rehabilitation and Patient Follow-up Methods.** International Medical Education Corporation at St. Francis Hotel, San Francisco. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

March 16-18—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Marriott Hotel, Palm Springs. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

March 18-24—**Current Drug Usage in Cardiac Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine sailing at Maui, Molokai, and Lanai, HI. One week. 24 hrs. Contact: Richard F. Paris, MD. (208) 788-4995.

March 19-20—**Advanced Cardiac Life Support.** See Emergency Medicine, March 19-20.

March 24—**Reflections on Cardiac Surgery.** See Surgery, March 24.

March 30-31—**New Developments in Brain and Cardiac Resuscitation.** See Emergency Medicine, March 30-31.

April 18-20—**Moguls of Cardiology.** American Heart Association, Golden Empire Chapter at Caesars Tahoe, Lake Tahoe. Wednesday-Friday. Contact: AHA, Golden Empire Chapt., P.O. Box 160126, 1727 30th St., Sacramento 95816. (916) 454-0701.

April 28—**50,000 Open-Heart Operations.** See Surgery, April 28.

May 4-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Sheraton Palace, San Francisco. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

May 12—**Cardiac Surgery Research.** See Surgery, May 12.

May 18-20—**Decision Making in Congenital Heart Disease.** Children's Hospital and Health Center and Donald N. Sharp Memorial Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Sunday. 18 hrs. $350. Contact: Congenital Heart Disease, P.O. Box 9494, San Diego 92109. (619) 272-3126.

May 21-22—**Advanced Cardiac Life Support.** See Emergency Medicine, May 21-22.

EMERGENCY MEDICINE

January 16-20—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 36 hrs.

January 21-28—**Pediatric Emergencies.** See Pediatrics, January 21-28.

January 30-31—**Advanced Cardiac Life Support.** Emergency Care Education Center, Inc., Emergency Department Physicians, Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

January 30-February 3—**Topics in Emergency Medicine.** UCSF at Sheraton on the Wharf, San Francisco. Monday-Friday.

February 26-March 2—**Emergency Medicine: 1984 7th Annual UCD Winter Conference.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 7 hrs. $345.

March 4-9—**5th Annual Mammoth Mountain Emergency Medicine Ski Conference.** Medical Conferences, Inc., UCI and Orange County Emergency Department Nurses Association at Mammoth Lakes. Sunday-Friday. 20 hrs. $325. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 650-4156.

March 5-8—**22nd Annual Critical Care Medicine Symposium.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday. 25 hrs. $395.

March 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at La Jolla Village Hotel, La Jolla. Monday-Friday.

March 14-16—**Advances in Controversies in Acute Respiratory Failure.** California Thoracic Society at Santa Barbara Biltmore Hotel, Santa Barbara. Wednesday-Friday. Contact: CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 19-20—**Advanced Cardiac Life Support.** Emergency Care Education Center, Inc., Emergency Department Physicians, Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

March 30-31—**New Developments in Brain and Cardiac Resuscitation.** UCLA. Friday-Saturday. 13.5 hrs. $180.

April 7-14—**Critical Care Medicine.** USC at Mauna Lani, HI. One week.

(Continued on Page 132)

ZORprin® (ASPIRIN) ZERO ORDER RELEASE

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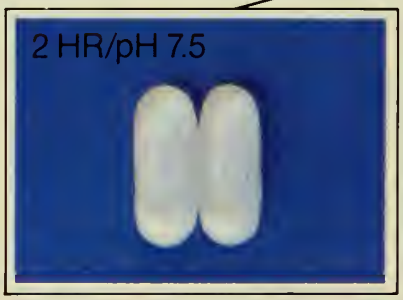

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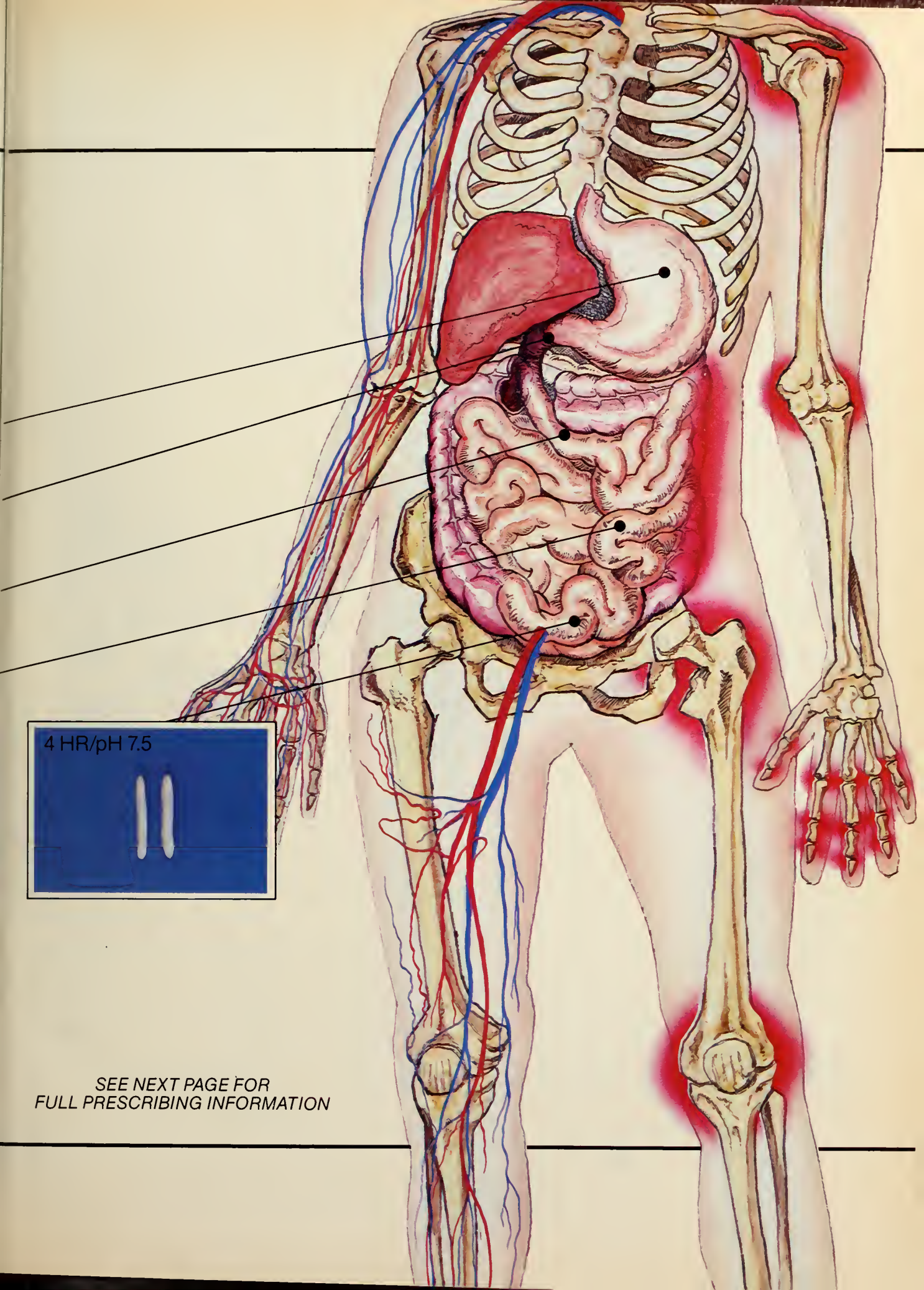

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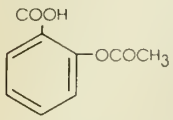
FULL PRESCRIBING INFORMATION

ZORprin (ASPIRIN) Zero-Order Release

DESCRIPTION: Each capsule-shaped tablet of Zorprin contains 800 mg of aspirin, formulated in a special matrix to control the release of aspirin after ingestion. The controlled availability of aspirin provided by Zorprin approximates zero-order release, the *in vitro* release of aspirin from the tablet matrix is linear and independent of the concentration of the drug. ☐ **CLINICAL PHARMACOLOGY**: Aspirin, as contained in Zorprin, is a salicylate that has demonstrated anti-inflammatory and analgesic activity. Its mode of action as an anti-inflammatory and analgesic agent may be due to the inhibition of synthesis of prostaglandins, although its exact mode of action is not known. ☐ Zorprin dissolution is pH-dependent. *In vitro* studies have shown very little aspirin to be released in acidic solutions, whereas, Zorprin releases the majority of its aspirin (90%) in a zero-order mode at a neutral to alkaline pH. It is this pH dependence of Zorprin that reduces direct contact between aspirin and the gastric mucosa, resulting in a reduction of its gastrointestinal side-effect potential. ☐ Bioavailability data for Zorprin have confirmed that plasma levels of salicylic acid and acetylsalicylic acid can be measured 24 hours after a single oral dose. This substantiates a twice daily dose regimen. Multiple dose bioavailability studies showed similar steady-state salicylate levels for Zorprin as for conventional release aspirin using the same total daily dose. Long-term monitoring of salicylate levels showed no signs of accumulation once steady-state levels were reached (4-6 days). ☐ Studies of *in vivo* prostaglandin levels (PGE2) have shown Zorprin plasma levels of salicylic acid and acetylsalicylic acid to reduce PGE2 levels 14 hours after a single oral 800 mg dose while an equivalent dose of aspirin produced a reduction of PGE2 levels only through six hours. Zorprin's effect on prostaglandins other than PGE2 has not been determined. ☐ Salicylates are excreted mainly by the kidney, and from studies in humans it appears that salicylate is excreted in the urine as free salicylic acid (10%), salicyluric acid (75%) salicylic phenolic (10%), acyl glucuronides (5%) and gentisic acid (<1%). ☐ **INDICATIONS & USAGE**: Zorprin is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of Zorprin have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care). ☐ In patients treated with Zorprin for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of Zorprin has been shown by reduction in pain, morning stiffness and disease activity as assessed by both the investigators and patients. ☐ In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Zorprin has been shown to be comparable to conventional release aspirin in controlling the aforementioned signs and symptoms of disease activity and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). Zorprin may be well tolerated in some patients who have had gastrointestinal side effects with conventional release aspirin, but these patients when treated with Zorprin should be carefully followed for signs and symptoms of gastrointestinal bleeding and ulceration. ☐ Since there have been no controlled trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of Zorprin in conjunction with other nonsteroidal anti-inflammatory agents (NSAI), the combination cannot be recommended (see **Drug Interactions**). ☐ **Because of its relatively long onset of action, Zorprin is not recommended for antipyresis or for short-term analgesia.** ☐ **CONTRAINDICATIONS**: Zorprin should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. Zorprin is not recommended for children under 12 years of age, it is contraindicated in all children with fever accompanied by dehydration. ☐ **WARNINGS**: Zorprin should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress platelet aggregation and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics, concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. ☐ While salicylates in large doses have a uricosuric effect, smaller amounts may reduce water excretion and increase serum uric acid. ☐ USE IN PREGNANCY: Aspirin can harm the fetus when administered to pregnant women. Aspirin interferes with maternal and infant hemostasis and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. ☐ If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. ☐ Aspirin should not be taken during the last 3 months of pregnancy. ☐ **PRECAUTIONS**: Appropriate precautions should be taken in prescribing Zorprin for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing Zorprin for those patients with bleeding tendencies or those on anticoagulants. ☐ In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when Zorprin is made a part of the treatment program. ☐ Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by dosage reduction. ☐ Salicylates can produce changes in thyroid function tests. ☐ Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. ☐ Since aspirin release from Zorprin is pH dependent, it may change in those conditions where the gastric pH has been increased as a result of antacids, gastric secretion inhibitors or surgical procedures. ☐ **Drug Interactions**: (See **WARNINGS**) Aspirin may interfere with some anticoagulant and antidiabetic drugs. Drugs which lower serum uric acid by increasing uric acid excretion (uricosurics) may be antagonized by the concomitant use of aspirin, particularly in doses less than 2.0 grams/day. Nonsteroidal anti-inflammatory drugs may be competitively displaced from their albumin binding sites by aspirin. This effect may negate the clinical efficacy of both drugs. Also, the gastrointestinal inflammatory potential of nonsteroidal anti-inflammatory drugs may be potentiated by aspirin. The combination of alcohol and aspirin may increase the risk of gastrointestinal bleeding. ☐ Aspirin may enhance the activity of methotrexate and increase its toxicity. ☐ Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Concomitant administration of other anti-inflammatory drugs may increase the risk of gastrointestinal ulceration. Urinary alkalinizers decrease aspirin's effectiveness by increasing the rate of salicylate renal excretion. Phenobarbital decreases aspirin's effectiveness by enzyme induction. ☐ **Pregnancy Category D**. See **WARNINGS** Section. ☐ **Nursing Mothers**: Salicylates have been detected in the breast milk of nursing mothers. Because of the potential for serious adverse reactions from aspirin in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the benefit of the drug to the mother. ☐ **ADVERSE REACTIONS**: **Hematologic**: Aspirin interferes with hemostasis. Patients with a history of blood coagulation defects or receiving anticoagulant drugs or with severe anemia should avoid Zorprin. Aspirin used chronically may cause a persistent iron deficiency anemia. ☐ **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from Zorprin is designed to occur in the small intestine over a period of time. This has resulted in fewer symptomatic gastrointestinal side effects. ☐ **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. Fatal anaphylactic shock, while not common, has been reported. ☐ **Respiratory**: Aspirin intolerance, manifested by exacerbations of bronchospasm and rhinitis, may occur in patients with a history of nasal polyps, asthma, or rhinitis. The mechanism of this intolerance is unknown but may be the result of aspirin-induced shunting of prostaglandin synthesis to the lipoxygenase pathway and the liberation of leukotrienes, e.g. slow-reacting substance of anaphylaxis. ☐ **Dermatologic**: Hives, rashes, and angioedema may occur, especially in patients suffering from chronic urticaria. ☐ **Central Nervous System**: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. ☐ **Renal**: Aspirin rarely may aggravate chronic kidney disease. ☐ **Hepatic**: High doses of aspirin have been reported to produce reversible hepatic dysfunction. ☐ **OVERDOSAGE**: Overdosage, if it occurs, would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Plasma salicylate levels in adults may range from 50 to 80 mg/dl in the mildly intoxicated patient to 110 to 160* mg/dl in the severely intoxicated patient. An arterial blood pH of 7.1 may indicate serious poisoning. The clearance of salicylates in children is much slower than adults and should receive due consideration when aspirin overdosages occur in infants, salicylate half-lives of 30 hours have been reported in infants 4-8 months old. Treatment for mild intoxication should include emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of sodium bicarbonate and dextrose or sodium lactate. In extreme cases, hemodialysis or peritoneal dialysis may be required. ☐ (*A plasma salicylate level of 160 mg/dl in an adult is usually considered lethal.) ☐ **DOSAGE & ADMINISTRATION**: *In order to achieve a zero-order release, the tablets of Zorprin should be swallowed intact.* ☐ *Breaking the tablets or disrupting the structure will alter the release profile of the drug.* ☐ *It is recommended that Zorprin be taken with sufficient quantities of fluids (8 oz. or more).* ☐ **Adult Dosage**: For mild to moderate pain associated with rheumatoid arthritis and osteoarthritis, the recommended initial dose of Zorprin is 1600 mg (2-800 mg tablets) twice a day. Because of Zorprin's prolonged release of aspirin into the bloodstream, Zorprin tablets may be taken as a b.i.d. dose. Further adjustment of the dosage should be determined by the physician, based upon the patient's response and needs. Since it will take 4-6 days to reach steady-state levels of salicylic acid with Zorprin, it is recommended dosages be given for at least one week before further adjustment. In general, patients with rheumatoid arthritis seem to require higher doses of Zorprin than do patients with osteoarthritis. ☐ **Zorprin is not recommended for children below the age of 12.** ☐ **HOW SUPPLIED**: **Zorprin Tablets 800 mg**; plain, white capsule-shaped tablets. ☐ Bottles of 100 Tablets — NDC 0524-0057-01. ☐ **Caution**: Federal law prohibits dispensing without prescription. ☐ U.S. Patent No. 4,308,251. ☐ **Manufactured and Distributed by: BOOTS PHARMACEUTICALS, INC., Shreveport, Louisiana 71106 U.S.A.** 12/8/83 0057-04

The structural formula of aspirin is.



Pioneers in medicine for the family

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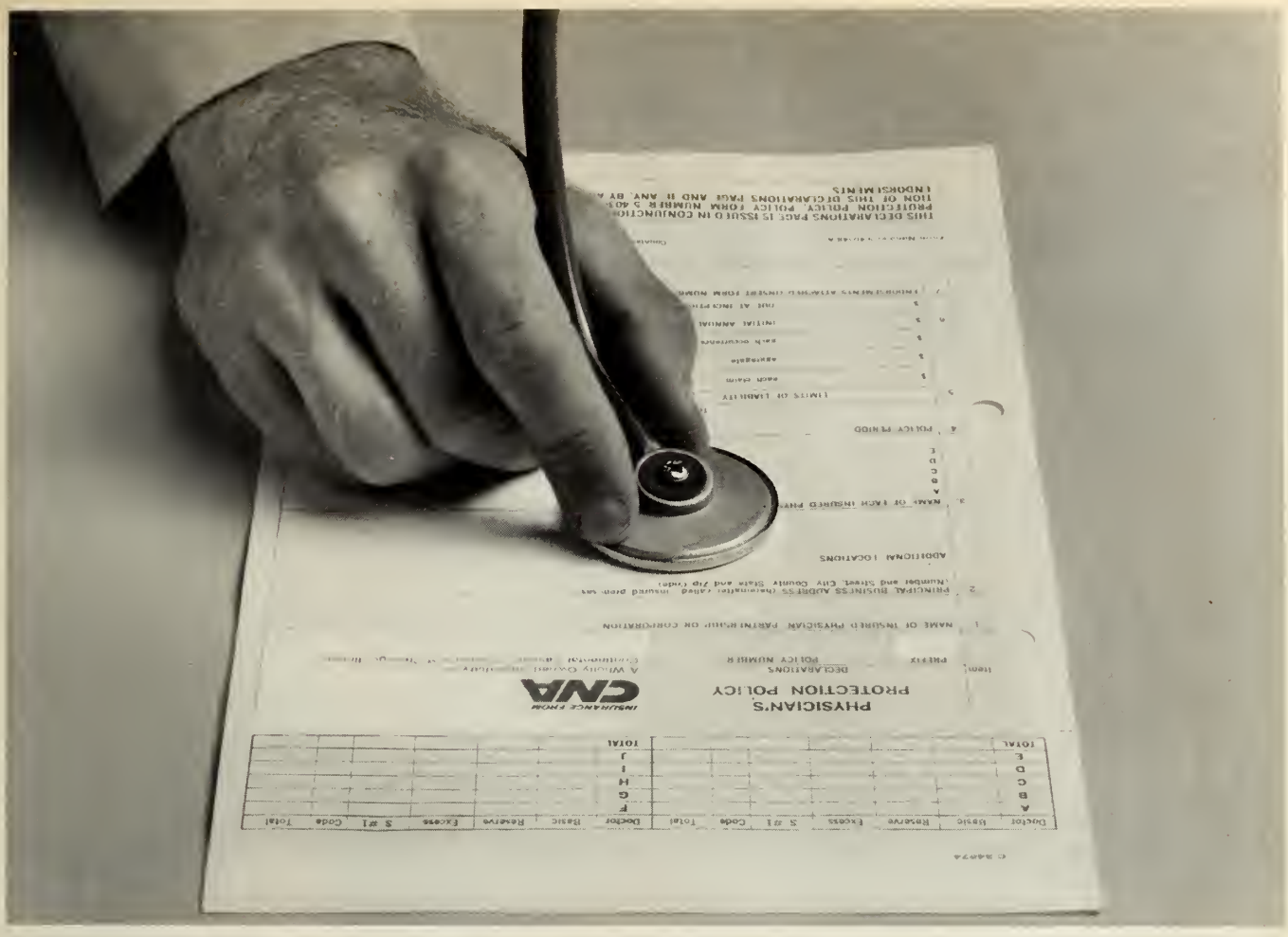

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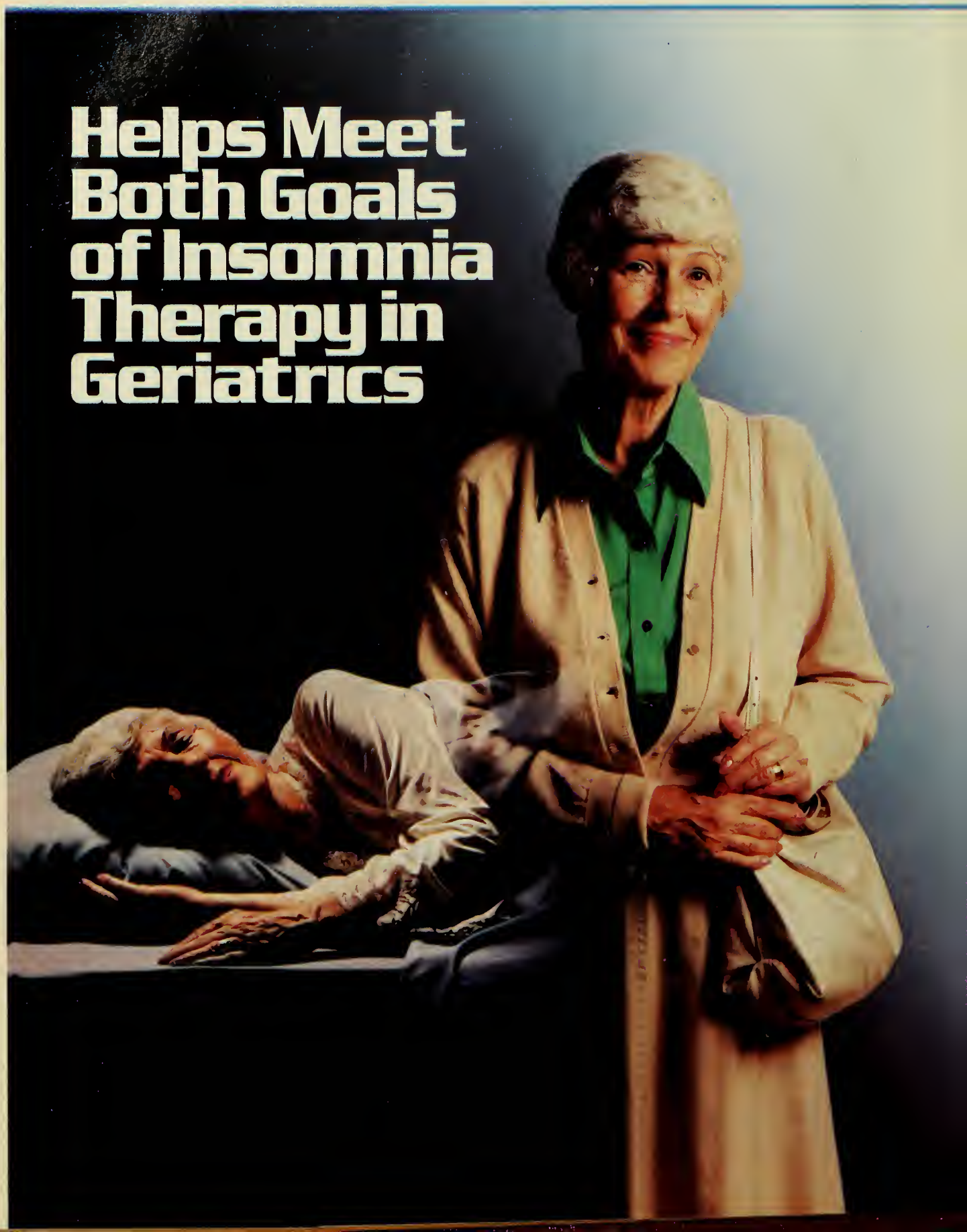
Halcion® 0.25 mg Tablets

triazolam CIV



Upjohn Please see next page for brief summary of prescribing information.

Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion

triazolam IV

0.25 mg Tablets
Initiate at 0.125 mg

© 1983 The Upjohn Company

Halcion Tablets
triazolam (IV)

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 198

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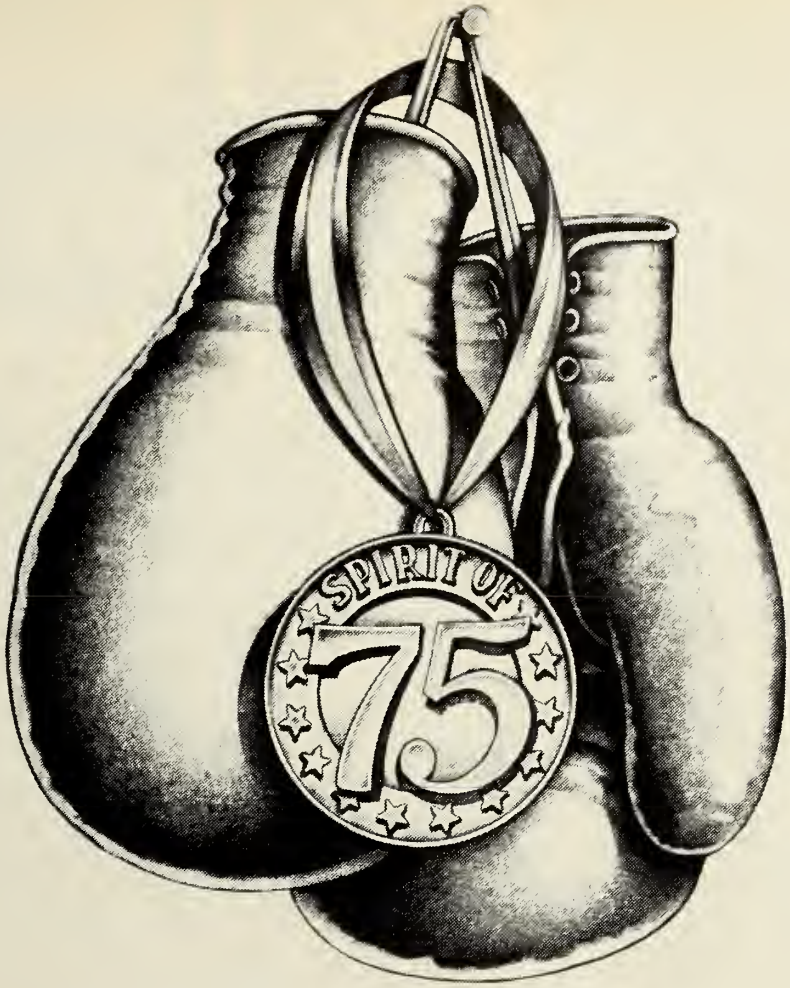

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The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County, Ventura County.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug [illegible] edema [illegible] requires therapy [illegible] combination regimen [illegible] dosage [illegible] use may be more convenient [illegible] patient [illegible] Treatment of hypertension [illegible] be reevaluated as [illegible]

Contraindications. [illegible] concomitant use with [illegible] such as spironolactone [illegible] severe renal or hepatic dysfunction [illegible] elevated serum potassium [illegible] other sulfonamide-derived drug [illegible]

Warnings: Do not use potassium supplements dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. [illegible] potassium tablets should [illegible] and has been associated with [illegible] likely in the severely [illegible] the elderly and diabetics with [illegible] sufficiency. Periodically [illegible] hyperkalemia develops [illegible] restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** [illegible] placental barrier [illegible] requires weighing [illegible] including total [illegible] adverse reaction [illegible] may appear in [illegible] should stop [illegible] available. [illegible] without a history [illegible] exacerbation [illegible] been reported with [illegible]

Precautions: [illegible] particularly [illegible] patient [illegible] serum [illegible] the elderly diabetics [illegible] with [illegible] patient [illegible] prompt [illegible] when treated with [illegible] Dyazide [illegible] require [illegible] intoxication [illegible] metabolic acidosis [illegible] Dyazide [illegible] Hypokalemia [illegible] Dyazide [illegible] taken such potassium supplements [illegible] intake of potassium-rich foods. Corrective measures [illegible] instituted [illegible] Discontinue [illegible] values reveal elevated serum potassium [illegible] occurs well [illegible] hypokalemia [illegible] triamterene may increase [illegible] serum PBI [illegible] Calcium excretion [illegible] be withdrawn [illegible]

[illegible] may add [illegible]

Adverse Reactions [illegible]

Supplied Dyazide is supplied as a maroon and white capsule in bottles of 1000 capsules. Single Unit Packages (unit-dose of 100 intended for institutional use only), in Patient-Pak unit of use bottles of 100.

The unique red and white Dyazide® capsule. Your assurance of SK&F quality.

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Triamterene sets 'Dyazide' apart from other diuretic products. This unique compound limits potassium loss usually associated with diuretic therapy, minimizing the potential for hypokalemic sequelae.

Potassium-Sparing

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

In Hypertension*...When You Need to Conserve K^+

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Serum K^+ and BUN should be checked periodically (see Warnings and Precautions)

Secondary Syphilis: Uncommon Manifestations a Common Disease

STEPHEN J. McPHEE, MD, *San Francisco*

Reports of cases of primary and secondary syphilis are increasing in the United States, particularly in urban areas and among homosexual men. While primary syphilis poses little diagnostic difficulty, many physicians are unfamiliar with the multisystem nature of secondary lues. Patients who have secondary syphilis commonly present with systemic signs, skin rash, mucous membrane lesions and generalized adenopathy. Less commonly, secondary syphilis may occur as acute meningitis, sensorineural hearing loss, iritis, anterior uveitis, optic neuritis, Bell's palsy, gastropathy, proctitis, hepatitis, pulmonary infiltration, nephrotic syndrome, glomerulonephritis, periostitis, tenosynovitis and polyarthritis. The diagnosis of secondary syphilis is easily confirmed. Its various manifestations are readily treated with penicillin and, if treated early, are entirely reversible. Two recent cases of secondary syphilis, one presenting as nephrotic syndrome and one as chorioretinitis and ptosis, illustrate the usual and unusual features of this common infection.

(McPhee SJ: Secondary syphilis: Uncommon manifestations of a common disease. West J Med 1984 Jan; 140:35-42.)

Syphilis currently ranks third in number of cases among reportable diseases in the United States. Cases of primary and secondary syphilis account for most of these reports, and the number has risen from 6,000 cases annually in 1957 to more than 27,000 cases in 1980.[1,2] Early syphilis is particularly common in the 20- to 24-year-old age group, among homosexual men and in urban areas.

Primary syphilis seldom poses diagnostic difficulty. The diagnosis is usually readily suggested by clinical findings familiar to most physicians. Secondary syphilis, however, may be misdiagnosed. Despite its frequency, many clinicians are unfamiliar with its protean multisystem manifestations. The unfamiliarity may lead to an inappropriately low degree of suspicion for a disease that is readily treatable and, if treated early, curable. Failure to suspect the diagnosis may subject patients to needless, expensive and potentially morbid investigation and delay therapy to a point where it is ineffective in preventing permanent sequelae.

I will describe two cases of secondary syphilis with unusual features and review the manifestations, diagnosis and treatment of this common disease.

Reports of Cases

CASE 1. The patient, a 30-year-old bisexual man, was seen in November 1981 because of fatigue, weakness, pharyngitis, nonproductive cough and mild gastrointestinal upset for three weeks. One month before being seen, he noted a flare of psoriasis and one week before, an acneiform rash on his chest. Ten days before presentation, a draining anal fistula occurred. His physician treated him with doxycycline hyclate given by mouth for five days; the fistula began healing. Two days later bilateral lower leg swelling and generalized myalgias developed. He had no urinary frequency, dysuria, oliguria or dark urine, but had noted urgency and excessively foamy urine. A 7-kg (15-lb) weight gain and increasing abdominal girth led to difficulty buttoning his trousers.

A hepatitis B infection two years previously had resolved without sequelae. An erythematous, papular rash a year before, diagnosed as guttate psoriasis, was

From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco.
Submitted, revised, April 11, 1983.
This study was supported in part by a grant from the Robert Wood Johnson Foundation.
Reprint requests to Stephen J. McPhee, MD, Division of General Internal Medicine, 400 Parnassus Avenue A405, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

FTA-ABS=fluorescent treponemal antibody absorption [test]
RPR=rapid plasma reagin [test]

treated with ultraviolet light and a topical steroid. Gonococcal exposure in the past had been treated with penicillin. He used no medicines and said he did not use intravenous drugs. His last sexual contact had been two months before.

On physical examination he was thin but well developed, with a temperature of 37°C, blood pressure 110/70 mm of mercury, pulse rate 72 per minute, respirations 16 and weight 69 kg (152 lb), 7 kg more than usual. There were about 20 well-circumscribed, 1-mm blanching, erythematous, papular lesions over the anterior thorax. A few shotty cervical and right axillary nodes were palpable. Mild left costovertebral angle tenderness and 1+ presacral edema were present. Both hemidiaphragms were elevated, but the lung fields were clear. The abdomen was mildly tender to deep palpation in the right midabdomen and epigastrium, without rebound or guarding. There was 3+ pitting edema to the knees bilaterally. The rest of the examination elicited no abnormalities.

The results of a complete blood count and serum electrolytes were completely normal. Other laboratory studies gave the following values: platelet count 524,000 per μl, erythrocyte sedimentation rate 113 mm per hour, serum creatinine 1.1 mg per dl, blood urea nitrogen 18 mg per dl, alkaline phosphatase 544 IU per liter, total protein 5.1 mg per dl and albumin 1.7 mg per dl. Urine analysis showed 4+ protein; 1+ heme; 25 to 50 leukocytes; less than 2 erythrocytes; a few granular, rare waxy and many hyaline casts, and oval fat bodies. No erythrocyte or leukocyte casts were identified. Hepatitis B-surface antigen test was negative. Throat culture showed no β-streptococci. A 24-hour urine collection showed 10.3 grams of protein and a creatinine clearance of 55.3 ml per minute.

A chest roentgenogram showed bilateral pleural effusions, a pyelogram done following intravenous administration of contrast material showed kidneys of normal size and function and a liver-spleen scan showed moderate hepatosplenomegaly without a focal defect. Urine culture was negative, stool culture showed mixed gastrointestinal flora and examination of three stool specimens for ova and parasites was negative. Serologic studies, including antinuclear antibody, rheumatoid factor, anti-double-stranded DNA antibody, serum complement (CH_{50}), immune complex assay, cytomegalovirus and antistreptolysin O titers were unrevealing. Serum protein electrophoresis showed hypoproteinemia (total protein, 4.7 grams per dl), hypoalbuminemia (albumin, 1.5 grams per dl) and slight elevation of α_2-globulins (1.3 grams per dl). A percutaneous renal biopsy was done on the sixth hospital day without complication. The specimen showed mild hypercellularity of the mesangial areas and membranous glomerulonephritis (Figure 1). There was immunofluorescent staining for immunoglobulin (Ig) G, IgM, IgA, C3 and C4 diffusely throughout the peripheral capillary walls of all glomeruli. The patient was treated with a low-salt, high-protein diet and diuretics.

The serologic test for syphilis (rapid plasma reagin [RPR]) done on admission subsequently returned positive at a titer of 1:512. The fluorescent treponemal antibody absorption (FTA-ABS) test was positive. A single intramuscular injection of 2.4 million units of benzathine penicillin G was administered without complication. Before the injection, the patient's serum

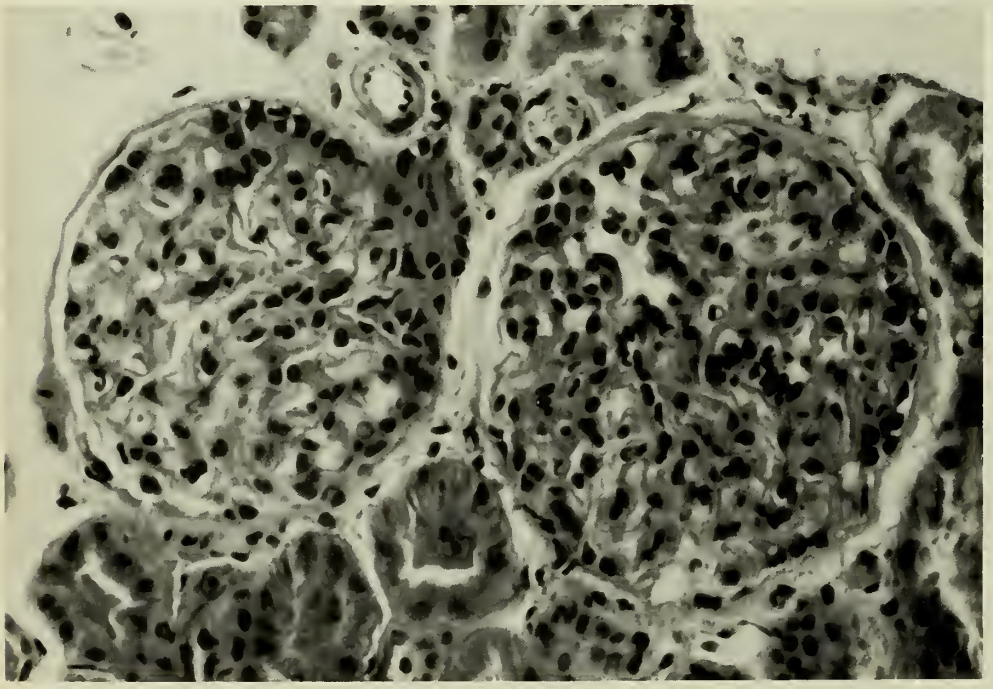

Figure 1.—Photomicrograph of renal biopsy specimen from patient in case 1, showing hypercellularity and endothelial and mesangial cell proliferation. (Reduced from magnification ×500.)

albumin level was 3.3 grams per dl, and urine analysis showed only 1+ protein. A 24-hour urine protein level was 0.97 grams. The patient was thus thought to be having spontaneous remission of his nephrotic syndrome.

Four days later, the patient felt better. His weight had fallen to 65 kg (144 lb) and on physical examination he showed only a trace of pedal edema. One month later he was entirely well, urine protein excretion was 0.11 grams per 24 hours and creatinine clearance was 140 ml per minute.

Comment. This bisexual man had secondary syphilis with typical luetic skin rash and adenopathy, and the unusual presentation of a nephrotic syndrome due to a membranous glomerulonephritis. The primary chancre was probably the anal lesion that was inadequately treated with oral doxycycline. The elevated serum alkaline phosphatase level may have represented syphilitic hepatitis. The patient underwent an extensive evaluation of his nephrotic syndrome, including renal biopsy, before the diagnosis of lues was established. He had spontaneous remission of the nephrotic syndrome and all other signs of the infection resolved after treatment with penicillin. One month later, his proteinuria had resolved and renal function returned to normal.

Case 2. The patient, a 27-year-old woman, was admitted in mid 1982 in the sixth month of pregnancy because of progressive bilateral loss of vision over the past six weeks and of palmar rash and fever for one week.

In February she had a cough productive of greenish sputum, sore throat, hoarseness and a fine red pruritic rash on the trunk and extremities that resolved spontaneously. She was diagnosed as having bronchitis and was treated with erythromycin, with little abatement of her symptoms. In March the pregnancy was discovered. In May a routine prenatal VDRL test was positive (titer 1:1,024) and the fluorescent treponemal antibody absorption test was positive. Because of a history of penicillin anaphylaxis, she was begun on a regimen of erythromycin, 500 mg four times a day for 15 days. One week later she awoke with a central visual defect in the right eye that progressed to almost total blindness. During the week before admission, headache, chills and fever to 38°C (101°F) developed. Despite continuing the erythromycin, she then had rapid loss of visual acuity in the left eye, a tender, maculopapular erythematous rash of both palms, increasing hoarseness, sore throat, neck pain and arthralgias in both arms.

An ophthalmologist diagnosed chorioretinitis and gave her a depot left periocular injection of corticosteroid to halt progression of visual loss. She was referred immediately to an infectious disease specialist who confirmed the presumptive diagnosis of secondary syphilis, and she was admitted.

Past medical illnesses included hepatitis, gonorrhea and herpes genitalis. Chronic intravenous narcotic abuse ended six months before her illness with enrollment in a methadone maintenance program. The patient had had bisexual activity since the death of her husband in April 1982.

On physicial examination she appeared chronically ill and was pregnant, with a temperature of 36.7°C, blood pressure 110/60 mm of mercury, pulse rate 80 beats per minute and respirations 16. There were multiple, tender, well-marginated, erythematous maculopapular lesions on both palms and soles with desquamation (Figure 2). The pupils reacted both directly and consensually. Both eyes showed evidence of chorioretinitis; both fundi were indistinct with pale yellow-gray retinae but no exudates (Figure 3). There was left periorbital edema and ptosis. Ulcerative lesions were visible on the medial nasal septum and hard palate. There was mildly tender, bilateral submandibular, anterior cervical, axillary and inguinal adenopathy. A grade 3/6 harsh systolic ejection murmur over the pulmonic area and an S4 gallop were heard. Examination of her abdomen showed a gravid uterus with a fetal heart rate of 132 beats per minute; there was no hepatosplenomegaly. Pelvic examination confirmed the fundal size to be consistent with an intrauterine pregnancy of 28 weeks' duration; there was mild right labial erythema without ulceration. There were old

Figure 2.—Photograph of multiple well-marginated, erythematous maculopapular skin lesions of the palm of the patient in case 2. Scrapings of similar lesions on the patient's sole examined by darkfield microscopy showed spirochetes.

needle tracks on both forearms. Findings on neurologic examination were nonfocal except for the left ptosis and pronounced bilateral visual impairment.

Laboratory studies showed mild anemia of pregnancy. Results of the urine analysis, serum chemistries and chest x-ray films were normal. The RPR test was positive with a VDRL titer of 1:1,024 and the FTA-ABS test was positive. Darkfield microscopy of scrapings from a lesion on the sole showed many spirochetes. Lumbar puncture yielded clear fluid with an opening pressure of 146 mm of water, and examination of the cerebrospinal fluid specimen gave the following values: glucose 44 mg per dl (serum glucose 104), protein 30 mg per dl, leukocytes 10 (6% polymorphonuclear leukocytes, 81% lymphocytes, 13% monocytes), no erythrocytes and VDRL positive at a titer of 1:4.

Other serologic tests, including hepatitis B-surface antigen, cytomegalovirus, rubella and toxoplasmosis, were negative. Cultures of cerebrospinal fluid, throat, urine and blood specimens were negative. An echocardiogram showed no valvular vegetations. A pelvic sonogram showed a single fetus of 27 to 28 weeks' size with a disproportionately large body size relative to head size, suggesting fetal hepatosplenomegaly or microcephaly (Figure 4).

A regimen of erythromycin, 500 mg given intravenously every six hours was immediately begun, while the patient underwent penicillin desensitization, which was accomplished without incident. The erythromycin was then discontinued and penicillin, 3 million units, was given intravenously every four hours. This therapy given for ten days produced no evidence of allergic or Jarisch-Herxheimer reactions.

Following initiation of penicillin therapy, there was gradual partial improvement of vision in both eyes. The left ptosis resolved, and there was marked diminution of skin rash and lymphadenopathy. Repeat pelvic ultrasound study one week later showed considerable reduction in the fetal head-body disproportion and subsequent ultrasound examinations were interpreted as normal (Figure 5). Following completion of the ten-day course of penicillin, the patient was discharged to her home city for careful follow-up.

Comment. This bisexual patient had typical luetic skin rash, mucous membrane lesions and adenopathy. After failure of oral erythromycin therapy, the infection spread to the central nervous system and the fetus. The central nervous system involvement of chorioretinitis and ptosis abated after high-dose penicillin therapy for neurosyphilis. Because of the delay in diagnosis and proper treatment, however, the patient may be left with permanent visual impairment. The long-term effects of the infection upon the pregnancy are unknown at this time.

Figure 3.—Fundus photograph of the right eye of the patient in case 2 showing diffuse haziness due to dustlike opacities of the posterior vitreous, as well as disseminated choroiditis with considerable retinal involvement.

Discussion

Untreated acquired syphilis progresses through several stages. Early or infectious syphilis consists of

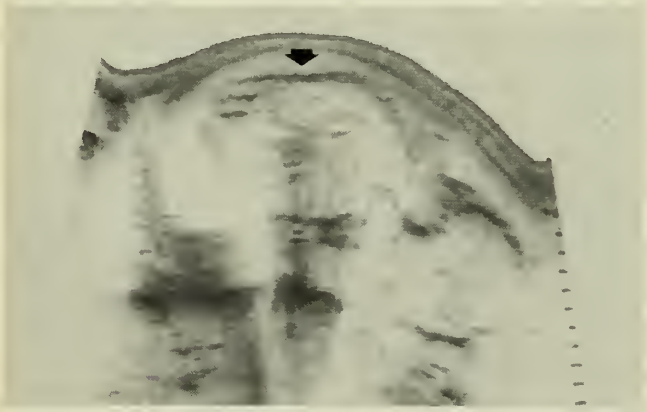

Figure 4.—Pelvic ultrasound examination done before treatment of the patient in case 2. The fetus, estimated to be 27 to 28 weeks gestational age, is in cephalic presentation. The body **(arrow)** is substantially larger than the head, which is concordant with femur length. Etiologic possibilities included microcephaly or hepatosplenomegaly. A small amount of fetal ascites is present.

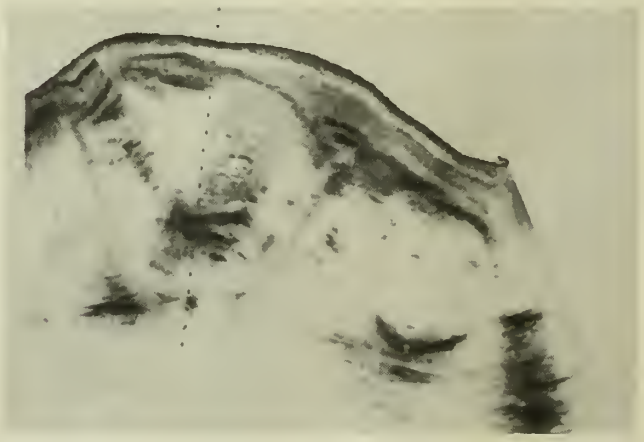

Figure 5.—Repeat pelvic ultrasound examination one month after treatment of patient in case 2. Since the previous examination, the body of the fetus has decreased in size; normal interval growth is shown. The fetal ascites has resolved.

a primary stage, characterized by the chancre and regional lymphadenopathy, and a secondary stage, characterized by mucocutaneous and multisystem involvement. In many cases, particularly among homosexual men, there may be no history of a primary lesion. Secondary syphilis appears about six weeks after spontaneous healing of the chancre. However, primary and secondary stages may overlap; up to 30% of secondary cases may have a healing chancre at diagnosis. The secondary stage lasts for two to six weeks, during which period the patient is highly infectious. Between 20% and 25% of untreated cases then relapse one or more times within a two- to four-year period, most often with anogenital and oral lesions. Spontaneous healing of these lesions occurs and a latent asymptomatic period follows. Finally, if no treatment has been given, about 25% of cases progress after a period of 5 to 30 years to the tertiary stage, with gummata, cardiovascular syphilis (aortitis) or neurosyphilis (tabes dorsalis and general paresis).[3-7]

Secondary syphilis has various systemic, mucocutaneous, neurologic, gastrointestinal, hepatic, pulmonary, renal and musculoskeletal manifestations.

Systemic Manifestations

Common systemic features of secondary lues include fever, malaise, anorexia, weight loss, headache and pharyngitis. Prolonged fever of unknown origin may occur.[8] Other systemic findings are splenomegaly, generalized (including epitrochlear) adenopathy and bone marrow involvement. A lymph node biopsy specimen typically shows nonspecific reactive follicular hyperplasia, which may extend into the medulla and resemble follicular lymphoma.[9] A bone marrow biopsy specimen may show striking though nonspecific plasmacytosis.

Mucocutaneous Manifestations

The mucocutaneous manifestations are an early and easily recognized feature of secondary lues, occurring in 80% of cases. Skin lesions are generally symmetric, nonpruritic and nonbullous. They may progress through four stages. Macular salmon pink or red lesions may be visible only in a bright light or following a warm bath. Maculopapular lesions (the "papulosquamous syphilid") may scale; they resemble psoriasis but involve the palms and soles. Papular indurated lesions may develop into necrotic, pustular lesions. In the rare case of syphilis maligna praecox, numerous nodular, pustular lesions of the trunk, extremities and oral mucosa evolve over several months into large necrotic ulcerations.[6] Alopecia, typically patchy and moth-eaten in appearance, may develop.

Mucous membrane lesions may take several forms. Condylomata lata appear in moist intertriginous areas such as the anogenital area. Beginning as eroded papules that may coalesce, they become hypertrophied cauliflower-like overgrowths. Split papules are similar lesions at the angles of the mouth. Mucous patches appear on the lips, tongue, buccal mucosa, pharynx, tonsils, vaginal introitus or glans penis. They are raised, round, painless gray plaques on an erythematous base; on the tongue, they appear as painless denuded areas. All mucous membrane lesions are highly infectious and tend to recur one or more times in untreated patients.[7]

Neurologic Manifestations

Neurologic features of secondary lues include acute meningitis, sensorineural hearing loss, iritis, anterior uveitis, optic neuritis and Bell's palsy.[10-14]

Although asymptomatic abnormalities of the cerebrospinal fluid may be found in up to 25% of patients with secondary syphilis, acute meningitis occurs in only 1% to 2%. Meningeal involvement may occur during initial rash, during mucocutaneous relapse or without rash. When meningitis occurs, it takes one of four forms: (1) aseptic meningitis with headache, nausea, vomiting, low-grade fever and meningismus; (2) acute syphilitic meningitis with meningeal signs and focal neurologic signs such as seizures, aphasia and hemiparesis; (3) acute syphilitic basilar meningitis with meningeal signs and asymmetric cranial nerve palsies, particularly of cranial nerves III, VI, VII and VIII, and (4) acute syphilitic hydrocephalus with papilledema.[6,10]

Acute, progressive, bilateral sensorineural hearing loss may occur in 20% of patients with acute syphilitic meningitis. Other cranial neuropathies may be associated.[12,13]

Iritis and anterior uveitis are heralded by photophobia, ocular pain and injection of scleral blood vessels. Optic neuritis, as in case 2, with greatly decreased vision and edema of the optic nerve head, occurs in up to 11% of patients with secondary lues.[11]

Cerebrospinal fluid findings of meningeal involvement include lymphocytic pleocytosis (100 to 1,000 mononuclear cells per μl), elevated protein level (50 to 200 mg per dl), depressed glucose level (in 50%) and positive VDRL tests. Spirochetes are present in the cerebrospinal fluid in 15% to 20% of cases.

Unlike longstanding tertiary syphilis, the meningeal findings of secondary syphilis usually respond completely to penicillin. Papilledema may require several months to respond, however. The hearing loss is reversible with early penicillin and corticosteroid therapy. Persistent eighth nerve deafness has been described.[13,14]

Gastrointestinal Manifestations

Gastrointestinal involvement in secondary syphilis may take several forms, including gastropathy, proctitis and hepatitis.

Syphilitic gastropathy probably occurs transiently in many patients who have secondary lues. As a persistent disorder it occurs in fewer than 1% of cases of late secondary lues. The clinical findings resemble those of peptic ulcer disease, but do not respond to standard ulcer therapy. Upper gastrointestinal tract x-ray studies early in the disease show multiple superficial ulcerations and hypertrophied, edematous rugae; later they may show a narrowed, nonpliable antrum.[15]

There are four endoscopically noted phases: an

ulcerative phase, an ulceronodular phase, a nodular, constrictive phase with a characteristic hourglass deformity and an infiltrative, fibrosing phase with a "leather-bottle" deformity resembling linitis plastica. A biopsy specimen shows shallow superficial ulcerations, dense mucosal monocytic and plasma cell infiltration, edema and characteristic proliferative endarteritis and panphlebitis.[16] Spirochetes may be found by silver or immunofluorescent antibody staining.[17] Both symptoms and x-ray findings resolve following penicillin therapy.

The diagnosis of syphilitic proctitis demands a high index of suspicion. The anal and rectal lesions occur following anal intercourse, and are seen most frequently among male homosexual patients.[18,19] The symptoms of rectal pain on defecation, mucoid discharge and blood-streaked stool may mimic those of hemorrhoids. Proctoscopy, however, reveals an irregular, indurated lesion with heaped-up margins and multiple small ulcerations.[20] A biopsy specimen shows a mononuclear cell infiltrate, vasculitis and, in some cases, spirochetes. The lesion responds rapidly to penicillin.

Syphilitic hepatitis, characterized by mild hepatic dysfunction and hepatomegaly, may occur in up to 10% of patients who have secondary lues.[21] Symptoms include malaise, anorexia, fever and chills. Jaundice is rare. Physical findings include hepatic enlargement and tenderness and occasional splenomegaly. Laboratory studies show mild elevation of serum bilirubin and transferase values and disproportionate elevation of serum alkaline phosphatase level up to ten times normal, as in case 1.[22-24] A liver biopsy specimen generally shows preservation of normal architecture but may show granulomatous hepatitis or focal hepatic necrosis with a nonspecific mononuclear and plasma cell infiltrate.[24,25] Despite the striking elevation of alkaline phosphatase level, unmistakable cholestasis is usually absent.[22-24] The finding of proliferative arteritis and phlebitis may provide a key to the diagnosis. Silver staining may show spirochetes. A repeat biopsy may show complete resolution of all changes as soon as two months after penicillin therapy.[25,26]

Pulmonary Manifestations

Pulmonary involvement occurs in 1% to 12.5% of autopsy studies of persons known to have had syphilis and is most common in cases of tertiary syphilis. When symptomatic, patients present with symptoms of bronchitis or pleurisy. Chest x-ray films show multiple nodular infiltrates, often at the lung bases. Following penicillin therapy, there is gradual though complete resolution over several months.[27,28] We have recently reported in this journal the case of a homosexual man with secondary syphilis and pulmonary manifestations.[29]

Renal Manifestations

Syphilitic nephropathy, though rare, may take one of several forms. Mild transient proteinuria may occur in some patients. In other patients, as in case 1, a clinically evident nephrotic syndrome develops. In these cases, there is no hematuria, hypertension or azotemia; oliguria and decreased *p*-aminohippuric acid and inulin clearances have been reported. Finally, acute hemorrhagic glomerulonephritis with gross hematuria, azotemia and hypertension has been reported.[30]

A renal biopsy specimen shows hypercellularity and endothelial and mesangial cell proliferation, as in case 1. Electron-microscopic study may show fusion of foot processes (similar to nil disease) and glomerular basement membrane subepithelial dense deposits. Recent immunofluorescence and elution studies have shown deposition of IgG, C3, treponemal antigen and antitreponemal antibody along the glomerular basement membrane.[31,32] In some cases, treponemes have been found. The prognosis is excellent. Spontaneous recovery, as in case 1, has been reported; otherwise, treatment with penicillin leads to rapid recovery. Chronic renal failure in treated patients has not been described.[30]

Musculoskeletal Manifestations

In as many as a third of patients with secondary syphilis, musculoskeletal complaints develop.[33,34]

Syphilitic periostitis and osteomyelitis are less common in secondary than in tertiary or congenital syphilis. Symptoms may be localized or diffuse bone pain, particularly nocturnal bone pain, relieved by movement and worsened by heat. On physical examination localized swelling or tenderness may be found. X-ray studies may show periosteal elevation, lytic lesions or pathologic fracture. Common sites of involvement include the skull (frontal bone), the shoulder girdle (distal clavicle) and the long bones (anterior tibia).[33] X-ray changes are uncommon in early secondary syphilis, but the findings on a bone scan using technetium Tc 99m may be positive before those of a plain radiograph.[34]

Nonmigratory symmetric polyarthritis may occur 3 to 12 weeks into the secondary stage. The polyarthritis most commonly involves the knee, ankle, sternoclavicular, wrist, metacarpophalangeal and proximal interphalangeal joints. Physical examination shows tenderness, synovial thickening and, in some cases, effusions. X-ray studies show only soft tissue swelling. A synovial fluid specimen in such cases shows a mild inflammatory response with 5,000 to 15,000 leukocytes per μl. A synovial biopsy specimen shows mild synovitis with acute and chronic inflammation and vascular congestion.[35]

A subacute tenosynovitis involving wrists and ankles presents with tendon sheath effusions without erythema, heat or tenderness. Gonorrhea must be excluded as the cause in such cases, since both venereal diseases may be contracted simultaneously.[35]

All of the musculoskeletal syndromes resolve rapidly after penicillin therapy.

Laboratory Diagnosis

Positive findings on darkfield microscopic examination are the quickest and most useful means to diag-

nose this highly infectious disease. Scrapings of material from any primary or secondary stage mucocutaneous lesion (chancre, condyloma latum, mucous patch) usually contain large numbers of spirochetes, as in case 2.[5] If the initial darkfield examination of a questionable lesion is negative, the patient should be instructed not to cleanse the involved area and to return for a repeat examination in 24 hours. Findings of darkfield microscopy of material from mouth lesions may be misleading due to the presence of saprophytic spirochetes, which are indistinguishable from *Treponema pallidum*.

Serologic tests are the most frequent means of diagnosing secondary lues. Two types of antibodies are produced: (1) nonspecific reagin or nontreponemal antibodies are IgG and M immunoglobulins directed against a lipoidal antigen that is produced by the interaction of *T pallidum* with host tissues, and (2) specific antitreponemal antibodies are immunoglobulins specific for *T pallidum*. The two types of serologic tests for syphilis correspond to these two antibody types.[36,37]

Routine screening tests use a cardiolipin-lecithin-cholesterol antigen to detect nontreponemal reaginic antibodies. The most widely used tests of this type are the VDRL (Venereal Disease Research Laboratory) slide flocculation test and the RPR agglutination test. If any reactivity is noted qualitatively on one of these screening tests, the patient's serum is serially diluted and the test repeated to quantitate the degree of reactivity. Reagin antibodies are first detected four to six weeks after infection, or about one to three weeks after the chancre appears. In untreated syphilis, the frequency of reactive screening tests depends on the stage of the disease. A reactive VDRL test is found in 67% of patients with primary syphilis, 99% to 100% of cases of secondary syphilis, 95% of those of early latent syphilis and 70% of late latent and tertiary syphilis. In secondary lues, the VDRL test titer is commonly quite high, usually 1:16 or more. A fourfold (or greater) decline in titer following therapy indicates adequate treatment of early syphilis. VDRL titers become nonreactive 6 to 12 months after treatment of primary syphilis, but may require 12 to 24 months for secondary lues.[38]

The most common specific test for treponemal antigen is the FTA-ABS test. In this test, a patient's serum is first absorbed with a nonpathogenic treponemal antigen. This removes cross-reacting antibodies to saprophytic treponemes. The absorbed serum is then layered on a slide containing dried *T pallidum*. If specific antibody to *T pallidum* is present, it adheres to the dried treponemes and is detected by fluorescence of the organisms upon adding fluorescein-labeled anti-human γ-globulin. As many as 1% of test results may be falsely positive when the FTA-ABS test is used to screen the general population. It is thus recommended as a confirmatory test when there is a high index of suspicion of syphilis clinically or, conversely, to determine a biological false-positive reaction following a nontreponemal test. Once reactive, the FTA-ABS test usually remains positive even after appropriate antibiotic therapy, and therefore it cannot be used to follow the response to therapy.[37]

A reactive VDRL test on a cerebrospinal fluid specimen is assumed to be indicative of active central nervous system infection. Because positive FTA-ABS test results have been found in the cerebrospinal fluid of patients with no evidence of neurosyphilis, the FTA-ABS test is not recommended for cerebrospinal fluid testing. In patients with secondary lues and no clinical evidence of neurologic involvement, cerebrospinal fluid examination need not be done if, following penicillin therapy, the VDRL test becomes negative or reaches and maintains a low titer within 12 to 24 months. A cerebrospinal fluid specimen should be examined if the VDRL titer does not become negative or decline by fourfold within 12 months of therapy, if the VDRL titer declines and then rises by fourfold or more or if clinical signs of mucocutaneous relapse occur despite treatment. In these circumstances, retreatment is indicated for treatment failure or reinfection, and the regimen used must depend on the cerebrospinal fluid findings. If they are abnormal, treatment for neurosyphilis is indicated.

Treatment

Because *T pallidum* is extremely susceptible to penicillin but grows and multiplies slowly, administration of sustained levels of parenteral penicillin G is the treatment of choice for secondary lues. The goal of therapy is to achieve and maintain serum penicillin concentrations of more than 0.03 μg per ml for 7 to 14 days. For primary, secondary and early latent syphilis, this may be achieved by a single intramuscular injection of 2.4 million units of benzathine penicillin G, or by eight daily intramuscular injections of 600,000 units of aqueous procaine penicillin G. Some authorities recommend the administration of 2.4 million units of benzathine penicillin G intramuscularly each week for two consecutive weeks for a total of 4.8 million units. With this regimen, Fiumara has reported no clinical or serologic failures, with all patients with a first attack of syphilis having prompt remission of symptoms and a nonreactive RPR test within 24 months.[39,40]

Other agents possibly effective in treating early syphilis include tetracycline, 500 mg given four times a day for 15 days, or erythromycin, 500 mg four times a day for 15 days.[41] As in case 2, however, not all patients will respond satisfactorily to such alternative therapy.

The treatment of neurosyphilis should involve higher doses of penicillin; it has been recently reviewed in this journal.[42]

Following administration of antibiotic therapy, some patients will experience the Jarisch-Herxheimer reaction, characterized by tachycardia, fever, chills, mild hypotension, malaise, headache, myalgias, sore throat, increased erythema of skin lesions and, rarely, jaundice. It may occur in as many as 50% of the primary

syphilis cases, 75% of secondary cases and 30% of tertiary cases. In general, no specific therapy beyond warning patients and administering an antipyretic is recommended. In a patient with serious neurologic manifestations, some authorities recommend treatment with aspirin or corticosteroids before administering antibiotic therapy.

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A Surgical Treatment for Snoring and Obstructive Sleep Apnea

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Snoring caused by oropharyngeal obstruction and some cases of obstructive sleep apnea syndrome can be cured or considerably lessened by resecting redundant tissue from patients' oropharynx and soft palate. Preoperative, and in some instances postoperative, sleep monitoring is a necessary part of evaluating these conditions.

(Simmons FB, Guilleminault C, Miles LE: A surgical treatment for snoring and obstructive sleep apnea. West J Med 1984 Jan; 140:43-46.)

Snoring is a symptom of an airway obstruction. Sometimes these obstructions are severe and herald obstructive sleep apnea, pulmonary and systemic hypertension and heart attacks. Other obstructions are mild and have no systemic sequelae; they are socially awkward but physically harmless. In this article we describe a surgical cure for some people in both groups.

Snoring can cause certain social problems. Sleeping in separate bedrooms, for example, is not healthy for a marriage. With some exceptions, there was no cure for heroic snoring in either risk group until about three years ago. Fujita and co-workers then introduced their uvulopalatoplasty operation based on earlier work done in Japan.[1] The theory behind this operation is that obstruction and turbulence in the airway are largely due to redundant tissue in the oropharynx, mainly in the soft palate. During deep sleep, oropharyngeal muscle tonus relaxes and these tissues collapse inward, creating the obstruction. On inspiration, the tissues vibrate, producing the snoring sound. Removing redundant soft palate and lateral pharyngeal walls clears both the obstruction and the turbulence.

The difference in success between this procedure and surgical models tried earlier seems to depend on the amount of tissue removed: excising only a large uvula, as was previously done, did not solve the problem.

We tried this procedure at Stanford for the same reason as Fujita and colleagues; it was an alternative for tracheotomy in the treatment of obstructive sleep apnea.[2] Of the more than 60 operations we have done, about 45% have relieved patients with obstructive sleep apnea of their clinical and laboratory abnormalities. Even in those cases in which important nighttime sleep abnormalities caused by oxygen desaturations or arrhythmias persisted, few had problems with snoring afterwards.

We have subsequently used this procedure successfully to give relief to persons with social snoring problems who had no other symptoms of overt sleep apnea. Here, we review the criteria for doing palatopharyngoplasty and present the results of these operations. They may apply to any patient whose primary symptom is snoring.

Indications for Surgical Treatment

It is most important to eliminate the possibility that obstructive sleep apnea is causing snoring. All apnea patients snore, but not all snorers have apnea. Apnea patients will have excessive daytime sleepiness, dozing off at inappropriate times—at conferences, while watching TV, while driving an automobile and so forth. They find it easy to go to sleep at night but difficult to get going in the morning. They commonly suffer from impotence, morning headaches, mental dullness and more than an average number of nightmares. Their sleep is characterized by excessive movement and their breathing by rhythm irregularities—periods of no breathing or gasps, of which they themselves are totally unaware. Most are overweight men and about half suffer from hypertension. There is considerable circumstantial evidence that obstructive sleep apnea is preceded by several years of simple snoring without other symptoms.

In addition, physicians must identify the anatomic structures most likely to be causing the snoring. The question, Where does the sound seem to be coming from? is a useful one. The snorer's bed partner can

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locate the source of the snoring within the vocal tract with a fair degree of accuracy: nasal, oropharyngeal or hypopharyngeal. That source can also be confirmed by a physician by tape recording the patient at home during sleep with a microphone placed about 0.5 m (18 in) from the mouth.

The palatopharyngoplasty operation is most successful with oropharyngeal-palatal snorers. Nasal snoring (a less common type of snoring) can be helped, but not by this operation. Few base-of-tongue (hypopharyngeal) snorers are good candidates for palatopharyngoplasty. Some have been helped by a type of operation that advances the mandible, but no results have been published to document the success rate of

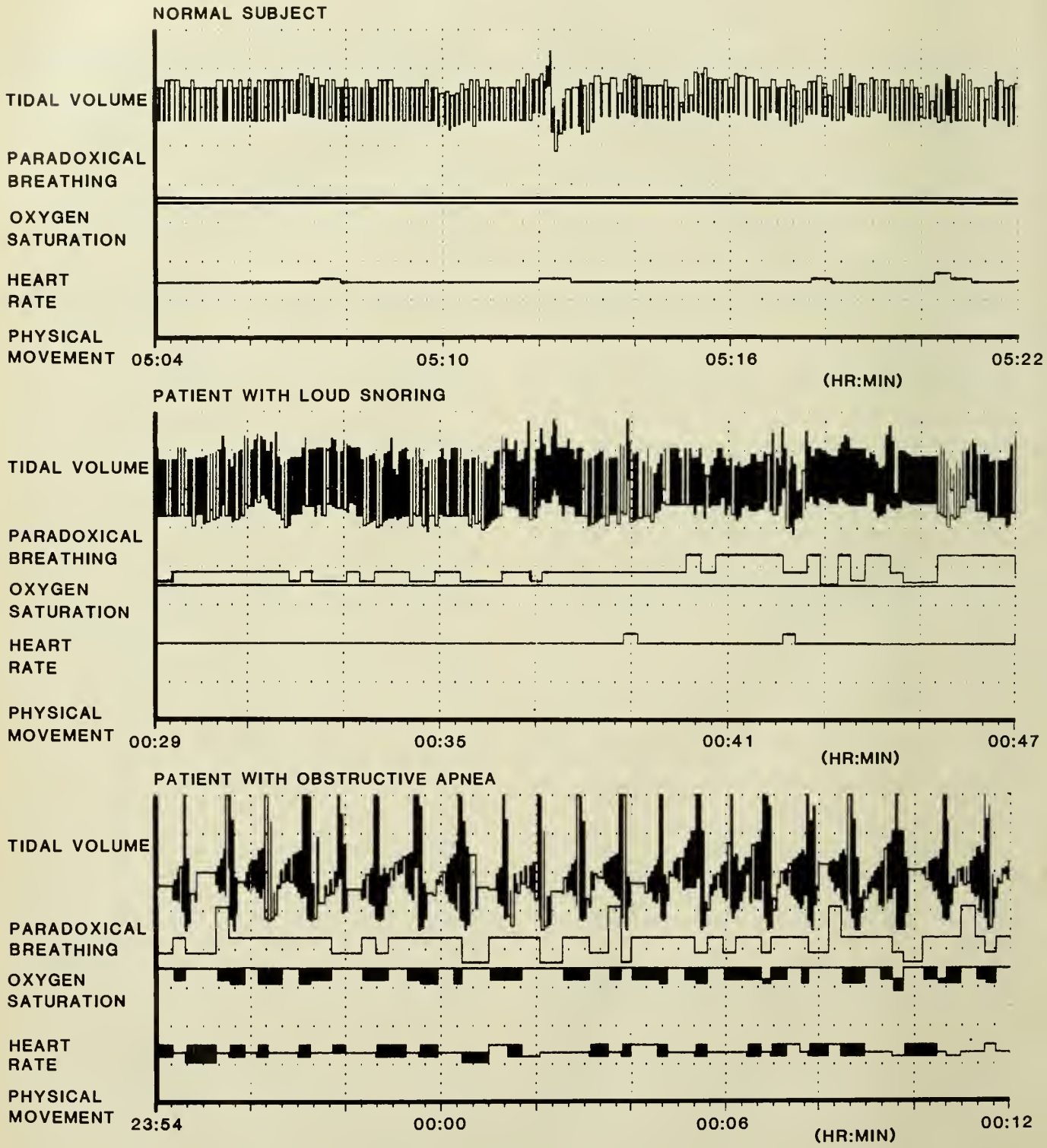

Figure 1.—Measurement of paradoxical breathing, oxygen saturation, heart rate and physical movement during sleep, using a Vitalog PMS-8 recording device, for a normal subject, a loud snorer and a person with obstructive apnea.

such operations. Those whose condition stems from the hypopharynx usually only snore on their backs. A bed partner's nudge solves the problem temporarily. This is not the case with those who have oropharyngeal snoring obstructions, who will snore in any body position. A nudge or position change will have no effect unless the person awakens.

Oropharyngeal snoring is typically the loudest of the three types. A relaxed palate acts as a vibrating air foil and is capable of remarkable intensities. Oropharyngeal snoring is graded in social severity according to how far away people complain. Most such persons are one- or two-bedrooms-away snorers but one-apartment or one-house-away snorers are not uncommon.

Physical examination is generally not enough to predict who snores and who does not. However, any partial airway obstruction can cause snoring. The upper airway should be thoroughly examined for neoplasms, cranial nerve paralysis and, especially in children, large tonsils. Tonsillectomy is definitely indicated for any child who snores.[3]

Although snoring is not confined to either sex or a particular body habitus, most snorers are modestly overweight, middle-aged men. (Losing weight will almost never stop the snoring but can attenuate it.) About half have mild hypertension.[4] An unusually long soft palate and a fairly narrow oropharyngeal inlet caused by redundant lateral mucosa is seen in almost half of the patients, whether or not they have tonsils. Redundant mucosa or large lingual tonsils, or both, can extend into the hypopharynx and obscure mirror examination of the larynx. The chances are very good that if the vocal cords cannot be seen because of this redundant tissue the patient has obstructive sleep apnea and should be referred for a complete sleep evaluation before palatopharyngoplasty is contemplated.

All patients who are being considered for this surgical treatment should undergo some form of nighttime sleep monitoring to gauge the severity of the airway obstruction and to rule out obstructive sleep apnea. If a patient has symptoms strongly suggestive of sleep apnea, referral to a sleep center is mandatory. If these symptoms are not present, or very mild, then a nighttime Holter electrocardiogram or preferably a Vitalog monitor (Vitalog Corp, Palo Alto, California) will allow the patient to be screened at home.

Figure 1 shows data obtained during sleep, using a Vitalog monitor, from a normal subject, a patient with loud snoring and a patient with obstructive sleep apnea who also snores loudly. The top trace shows a continuous record of absolute tidal volumes measured by means of calibrated Respitrace (Ambulatory Monitoring Inc, Ardsley, NY) sensors. In the normal person there is a regular tidal volume of about 500 ml, except for a period of brief arousal at 5:12 AM. In the patient with snoring the tidal volume is greater and the breathing is more erratic. In the patient with obstructive apnea, the tidal volume shows wild swings, including epochs of zero airflow due to complete obstruction.

The second trace shows the occurrence of paradoxical breathing; that is, a *reduction* in the volume of either chest or abdominal (diaphragmatic) compartment when there is a net *increase* in total lung volume; or, an *increase* in volume of either chest or abdominal compartment when there is a net *decrease* in lung volume. During sleep, such changes are almost always a sign of significant airway obstruction. In obstructive apnea, or obstructive hypopnea, there is relatively increased respiratory effort and paradoxical breathing, though for much of the event true effort may be reduced or even absent as respiratory muscle fatigue is manifest. Note that the patient who has loud snoring (but no overt apnea) still shows evidence of significant respiratory obstruction.

The third trace, blood oxygen saturation, remains stable and normal in the normal subject and in the person with snoring, but oscillates from normal to less than 60% in the patient with obstructive apnea. Although oxygen recordings are accurate and reliable, currently available oximeters are rather cumbersome for home use. Local steady-state heart rate, the fourth tracing, is stable in normal sleep and in most patients who have simple snoring, but in cases of obstructive apnea shows a characteristic change (bradytachycardia) that is usually (but not invariably) associated with each episode of obstructive sleep apnea. The bottom trace, though it shows no body movements in these examples, often displays significant activity in patients with obstructive apnea as they struggle to breathe.

An overnight tape recording of an electrocardiogram alone can also be used to detect bradytachycardia, but this change is not an invariable feature of sleep apnea.

Any patient with repetitive episodes of apnea or hypopnea lasting more than 20 seconds with partial arousal from sleep and oxygen saturations less than 85% or a cyclic profound bradycardia (40 beats per minute or less) should be referred to a sleep disorders center for more comprehensive evaluation. Patients with minimal evidence of complete airway obstruction need not be referred but should be monitored again three to six months after a palatopharyngoplasty.

Description of Palatopharyngoplasty and Results

The surgical approach in this procedure is similar to that of a tonsillectomy under general anesthetic. The thin posterior half of the soft palate is removed completely, then the tonsils or the mucosa and some underlying muscle from the tonsillar fossa are excised. As much excess lateral posterior wall tissue is removed as possible. The margin of the posterior-lateral pharyngeal mucosa and constrictor muscle is sutured laterally to the remaining edge of the anterior tonsillar pillar. The raw edges of the soft palate are then sutured together.

We have done this operation on 60 apnea patients and 10 simple snoring patients as of October 1982, with few postoperative complications. None of the patients have had airway problems. A tracheotomy was done concurrently on six of these patients, all of whom had moderate to severe obstructive sleep apnea. In

TABLE 1.—*Summary of 20 Cases in Which Palatopharyngoplasty Was Done*

		Preoperative Studies		*Postoperative Studies*		
Results		*Oxygen Saturation % (Range)*	*Apnea Index % (Range)*	*Oxygen Saturation % (Range)*	*Apnea Index % (Range)*	*Patient's Opinion of Clinical Success*
Condition improved	(N= 9) ...	53 (19-94)	40 (14-63)	87 (77-90)	15 (1-39)	100% Cured
Condition not improved	(N=11) ...	58 (26-82)	50 (13-79)	58 (24-80)	40 (9-80)	27% Cured 46% Improved

each instance it was felt that the cure we anticipated from the palatopharyngoplasty alone did not justify delaying tracheotomy. All patients had a very sore throat afterwards, lasting at least a week. The duration of hospital stay depended strictly on a patient's ability to maintain oral fluid intake; it was usually three to four days. About a fourth of the patients had occasional nasal regurgitation of fluids for one to two months. None felt this was an important problem. Four patients continue to have minor episodes of nasal regurgitation but all of them prefer this minor discomfort to their previous symptoms. None have had changes in their speech. The lack of hypernasality is surprising to us because good velopharyngeal closure should not be occurring in some of these patients based on clinical considerations.

Preoperative snoring symptoms ceased or were considerably attenuated in all patients. This impressive statistic is the result of reports from the patients or their bed partners, and not from direct observation. All ten of the simple snorers and at least 80% of the sleep apnea patients felt the quality of their sleep was much improved and that they felt better in the daytime. There is reason to be a little suspicious of claims of improvement from patients suffering from sleep apnea, because some of these people knew that if the palatopharyngoplasty was unsuccessful they would face a tracheotomy. In addition, two of these patients were observed snoring during their follow-up sleep studies, and both were eventually recommended for tracheotomy. On the other hand, it has been a real problem getting many of the sleep apnea patients to return for a follow-up sleep study because of improved clinical symptoms. This is clearly a mistake, as Table 1 shows. Although all of the simple snorers were helped, in only about half of the apnea patients were results totally successful.

The data summarized in Table 1 are from the sleep studies of the first 20 patients on whom we were able to obtain postoperative measures at four to six months. Nine were considered cured on the basis of achieving normal levels of minimum oxygen saturation during sleep of 85%, or an improvement of at least 35 percentage points from their preoperative levels. Eleven failed by the same criteria. The apnea index is the average number of episodes of apnea and hypopnea per hour of sleep. Normal is 5 or less. Note that even in the successful group, not everyone achieved normality.

We have already mentioned that a patient's opinion of symptom relief—usually based on daytime sleepiness in apnea patients—can be misleading. We eventually recommended tracheotomy for four patients who considered themselves cured or much improved. There is no question that even the patients with poor results do feel better because there are fewer arousals during their sleep.

Findings for the group of patients who snored but had no obstructive apnea are not shown in Table 1 because their apnea indices were normal—5 or less—and oxygen saturation did not drop below 85% in those few who did have preoperative sleep studies. The others were judged to be simple snorers because they had none of the other symptoms of sleep apnea.

Conclusion

Palatopharyngoplasty successfully treats uncomplicated oropharyngeal snoring. It has mixed results in treating obstructive sleep apnea. Some patients appear to be poorer risks than others because of massive obesity, smaller than normal mandibles or excessive hypopharyngeal tissue that is technically difficult to remove by a transoral approach. When these and other problems can be solved surgical results should improve. It is unlikely that the need for a permanent tracheotomy can be completely eliminated in the near future.

We are now recommending all patients we are considering for this operation, even those without apnea symptoms, to receive screening sleep monitoring. There are two reasons for this recommendation. First, it is important to know the physiologic effects of all partially obstructed airways. As we have come to understand, patients do not always recognize (or admit to) problems beyond snoring and such patients at the very least will need closer follow-up than those who are completely normal by monitoring. Second, insurance companies have been understandably reluctant to reimburse an operation to cure snoring. They take the position that this procedure is "cosmetic." They are unlikely to change that attitude without having solid data from a monitor showing an airway obstruction.

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Sulfisoxazole Chemoprophylaxis and Recurrent Otitis Media

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Sulfisoxazole, 75 mg per kg per day, was administered for 13 weeks to all children with otitis media recurring at a rate of at least once every other month. The first 26 patients began prophylaxis during the months of January and February of 1979. To compare rates of otitis media with those in children not receiving concurrent prophylaxis during the same season, a matched control was randomly chosen as a child who began prophylaxis on the day nearest that when a study patient completed prophylaxis. The rates of otitis media during this same period were determined as the number of episodes per patient-month. Of the 26 treated patients, 11 had 16 episodes of otitis media in 72 patient-months (0.22 episodes per patient-month), in contrast to the 26 untreated patients who had 63 episodes in the same period (0.88 episodes per patient-month). This 75% reduction in incidence was statistically significant by χ^2 analysis ($P<.005$). The two groups of children were comparable in age, sex, nursery school attendance, family history of allergy and number of episodes in the three months preceding chemoprophylaxis. These findings support the short-term chemoprophylactic use of sulfisoxazole for recurrent otitis media.

(Liston TE, Harbison R: Sulfisoxazole chemoprophylaxis and recurrent otitis media. West J Med 1984 Jan; 140:47-49.)

Children who have recurrent otitis media during early childhood manifest learning disability on entering school.[1] In the absence of proved benefit from other various medical and surgical treatments, chemoprophylactic administration of antibiotics has been recommended.[2,3] In repeating the double-blind crossover study of sulfisoxazole chemoprophylaxis reported by Perrin and co-workers,[4] we found a statistically significant difference in the rates of otitis media in patients beginning with placebo first but nearly identical rates in the group beginning with sulfisoxazole first, which suggested a carryover effect—that is, the patients continued to benefit from treatment after use of the active agent was discontinued.[5] Because of these findings, we concluded that the crossover design did not provide an adequate way to evaluate this form of management. As a result, we have evaluated similarly treated patients using untreated, matched controls instead.

Patients and Methods

The patients in this study were selected from a population of children with recurrent otitis media who were referred to—and were followed by—the primary author (T.E.L.) on a continuing basis at Wilford Hall USAF Medical Center, Lackland Air Force Base, Texas. Referrals from the general pediatric clinic number about 150 children per year. Patients were examined whenever a parent suspected an ear infection because of signs such as rhinitis, irritability, fever or indication of ear pain. Acute otitis media was diagnosed in such children when pneumatic otoscopy showed bulging of the pars flaccida with obliteration of bony landmarks through a dull or red tympanic membrane in which there was decreased mobility. Serous otitis media, characterized by retraction of a translucent tympanic membrane with prominent bony landmarks, was distinguished from acute episodes of otitis media. Beginning in January of 1979, chemoprophylactic ad-

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TABLE 1.—*Effectiveness of Chemoprophylactic Administration of Sulfisoxazole*

Groups	*Number*	*Months*	*Episodes of Otitis Media*	*Rate*
Study patients	26	72	16	0.22*
Control patients	26	72	63	0.88*

*$\chi^2=27.96$; $P<.005$.

TABLE 2.—*Epidemiologic Comparison for Otitis Media*

Factors	*Study Patients*	*Control Patients*
Age (mean yr)	1.4	1.6
Male:female ratio	1:1	1.3:1
Nursery school	11	12
History of atopy	14	16
Number of episodes in the preceeding 3 months		
1-2	12	12
3-4	14	14
Total number of patients	26	26

ministration of sulfisoxazole became standard therapy for children who had three or more episodes of otitis media occurring at a rate of at least one every other month. All in this report who qualified for treatment were children younger than the age of 5 years who had had no previous operation, cleft palate or known immunodeficiency.

In all, 27 consecutive patients began receiving sulfisoxazole therapy, 75 mg per kg per day in two divided doses, during the months of January and February, 1979. One patient was excluded from the study when chemoprophylaxis was discontinued because of urticarial rash. The remaining 26 patients were treated for 13 weeks unless two episodes of otitis media occurred, at which time prophylaxis was discontinued and the patient was referred for tympanostomy tube placement. Prophylaxis was discontinued during treatment of an acute episode; treatment usually consisted of amoxicillin trihydrate, 40 mg per kg per day. Erythromycin, 40 mg per kg per day, and sulfisoxazole, 150 mg per kg per day, were prescribed for those who were allergic to penicillin or who failed to improve by the follow-up visit after 72 hours of therapy. After responding successfully, patients completed a ten-day course of therapy and then were restarted on a chemoprophylaxis regimen. Patients were considered to be receiving prophylaxis during the time they were treated for such episodes.

The patients who served as controls were children who had recurrent otitis media by the same criteria but who had not yet begun prophylaxis. Each child selected as a control had begun chemoprophylaxis on the day nearest that when a study patient had finished prophylaxis. Thus, the control patient was evaluated retrospectively for episodes of otitis media that occurred during the same weeks that the study patient was receiving chemoprophylaxis. Both study and control patients began prophylaxis immediately after finishing successful treatment for the qualifying episode. Data recorded in the charts of all patients included age, sex, number of episodes in the 13 weeks preceding treatment, nursery school attendance (three days or more a week), family history of allergic rhinitis or asthma and response to chemoprophylaxis in the first and second halves of this therapy. Patients were questioned monthly about any apparent side effects. All data for both groups were collected by retrospective chart review, and statistical comparisons were made by χ^2 analysis in the usual manner by squaring the difference for each cell and dividing by the frequency expected.

Results

The 26 study patients received sulfisoxazole for 312 weeks (72 months). Three patients, who had two episodes of otitis media during chemoprophylaxis, were referred for tympanostomy tubes before completing the full three-month observation period, and two left the area after completing ten weeks of follow-up. During this time, 11 patients had 16 episodes of otitis media, yielding a rate of 0.22 episodes per patient-month. In contrast, the 26 untreated matched control patients had 63 episodes during the same period, yielding a rate of 0.88 episodes per patient-month. This 75% reduction in incidence of otitis media is statistically significant ($P<.005$) (Table 1). The 21 patients who completed the entire study had nine episodes in 62 months (0.15 episodes per patient-month) in contrast to their controls, who had 51 episodes during the same period (0.82 episodes per patient-month), which represents an 82% reduction ($\chi^2=29.40$, $P<.005$).

Each control patient started the chemoprophylaxis regimen within five days of a study patient who was completing chemoprophylaxis (mean difference, 1.9 days). The mean age of the study patients was 1.4 years and of the control patients was 1.6 years. Equal numbers of boys and girls were in the study group; three more boys than girls were in the control group. One more patient in the control group than in the study group attended nursery school; similarly, one more in the control group had a family history of atopy. By chance, the number of episodes of otitis media in the three months (13 weeks) preceding chemoprophylaxis was identical in each group: 67 episodes in 78 months or 0.86 episodes per patient-month (Table 2).

The rates of otitis media in the study and control patients were calculated for the epidemiologic factors listed and for both first and second halves of the study period (Table 3). There was at least a 60% reduction in the rate of otitis media between the treated and the untreated groups regardless of the factor evaluated. The difference in rate of otitis media in children receiving chemoprophylaxis compared with the difference in those who were not was more significant in children younger than 2 years, in boys, in those with at least three episodes in the preceding three months, in those who attended nursery school and in those with a family history of allergy. The ratio of the rate while receiving chemoprophylaxis to that while not was almost identical in the first half of the study (27%) compared with the same ratio in the second half (25%). No side

TABLE 3.—*Epidemiologic Factors and Rates of Otitis Media*

Factor	*Study Patients*	*Control Patients*	*Percent Reduction*	*Significance* (χ^2, $P<$)	
Age					
0-1 yr	0.24	0.83	71	14.00	.005
2-4 yr	0.18	0.93	81	11.44	.005
Sex					
male	0.14	0.92	85	20.09	.005
female	0.28	0.81	65	7.56	.01
Preceding episodes					
0-2	0.24	0.62	61	6.53	.025
3-4	0.21	1.12	81	23.60	.005
Nursery school					
yes	0.06	1.04	94	29.28	.005
no	0.36	0.75	52	5.82	.025
History atopy					
yes	0.17	0.90	81	20.98	.005
no	0.28	0.83	66	8.68	.005
Time studied					
1st half	0.25	0.94	73	14.23	.005
2nd half	0.20	0.81	75	13.44	.005

effects from the prophylaxis were reported except in the single patient with urticaria, who was not rechallenged.

Discussion

We undertook the study to further evaluate the effectiveness of sulfisoxazole chemoprophylaxis in preventing otitis media in children. Perrin and colleagues,[4] in a crossover study conducted during the months of December through May, evaluated 36 children younger than the age of 6 years, who had 25 episodes of otitis media, 24 occurring while they took placebo. Although their results were statistically significant, the study's clinical importance may be questioned because the rate of otitis media while taking placebo was only 0.22 episodes per patient-month. With only one episode expected every 4.5 months, chemoprophylaxis administered for only three months might not exert noticeable benefit.

Using a similar dose of sulfisoxazole, we evaluated 35 patients younger than 5 years of age, using the same double-blind crossover design.[5] In qualifying for this year-round study, the 35 patients had 84 episodes in the 105 patient-months before entry (0.80 episodes per patient-month). Although the rate for chemoprophylaxis (0.25 episodes per patient-month) was statistically different ($\chi^2=4.76$; $P<.05$) from the rate observed while the same patients were taking placebo (0.42 episodes per patient-month), the differences were influenced by order of drug given. We observed a more significant difference between rates in patients treated with placebo first (0.20 with sulfisoxazole versus 0.56 with placebo; $\chi^2=7.13$, $P<.001$) but not in those given the active drug first (0.28 versus 0.30; not significant). Thus, we concluded from the previous study that patients did not adequately serve as their own controls.

The response to chemoprophylaxis in the 26 patients in the present study (0.22 episodes per patient-month) was similar to that observed in our previous study and significantly less than the rate of the matched controls (0.88 episodes per patient-month). Except for a better response in those attending nursery school, no epidemiologic factor predicted favorable response. The control patients were similar to the study patients in that they had otitis media at a frequency qualifying them for chemoprophylaxis that was identical over a three-month period. The two groups were also similar in age, sex, nursery school attendance and family history of atopy. The study patients were chosen consecutively during the two high-risk winter months, and the control patients were matched solely by time of year to correct for the seasonal variation in expected rate of otitis media.

Our experience suggests that chemoprophylactic administration of sulfisoxazole significantly decreases the rate of otitis media in children who had episodes recurring at an incidence of almost one per month. The reduced rate of otitis media in patients receiving chemoprophylaxis—from 0.88 to 0.22 episodes per patient-month (75%)—is more than that found in a similar high-risk group treated with tympanostomy tubes, which yielded a reduction in rate from 0.36 to 0.11 episodes per patient-month (69%).[6] Chemoprophylaxis in the dose and duration described appears safe. Yet, because of the relatively large number of treatment failures, improved methods of management need to be investigated to improve outcome.

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Medical Progress

Abdominal Aortic Aneurysms

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Aneurysms are common in our increasingly elderly population, and are a major threat to life and limb. Until the advent of vascular reconstructive techniques, aneurysm patients were subject to an overwhelming risk of death from exsanguination. The first successful repair of an abdominal aortic aneurysm using an interposed arterial homograft was reported by Dubost in 1952. A milestone in the evolution of vascular surgery, this event and subsequent diagnostic, operative and prosthetic graft refinements have permitted patients with an unruptured abdominal aortic aneurysm to enjoy a better prognosis than patients with almost any other form of major systemic illness.

(Fortner G, Johansen K: Abdominal aortic aneurysms [Medical Progress]. West J Med 1984 Jan; 140:50-59.)

An aneurysm is a balloonlike dilatation of an artery that frequently presents as a pulsatile mass. Such lesions have long been recognized, classically in the extremities, as a result of infection or trauma. In the second century AD Antyllus gave a clear description of aneurysms, including a taxonomy related to such lesions' potential for rupture. Galen described aneurysms due to trauma, especially from an unskillful phlebotomy, and noted that rupture could be forestalled in some circumstances by external compression. In the fifth century AD Aëtius clearly described a now well-established principle of operative treatment of aneurysms in which proximal arterial control is followed by ligature from within the aneurysm of the orifices of inflow and outflow vessels. Vesalius offered the first clinical description of an aneurysm of the abdominal aorta, and his 16th-century contemporary Ambroise Paré pointed out that arterial wall degeneration can be caused by syphilis, that aneurysms may thrombose and that injudicious incision of an inflamed pulsatile mass may cause exsanguinating hemorrhage. Morgagni observed yet another complication of aneurysms—erosion of the vertebral bodies by a subjacent aortic aneurysm. William and John Hunter, who made significant advances in both the physiology and surgical repair of blood vessels, pioneered in the treatment of peripheral aneurysms, and John Hunter's work on collateral blood flow led to a much easier approach to these lesions—proximal arterial occlusion by ligature. One of Hunter's pupils, Sir Astley Cooper, used the Hunterian approach for common carotid and internal and external iliac artery aneurysms and in 1817 ligated the abdominal aorta proximal to a leaking left iliac artery aneurysm.

Aneurysms tend to enlarge, and their risk of rupture rises geometrically with their size. Numerous novel attempts were made to halt the inexorable growth of aneurysms in the decades before the development of modern vascular surgical techniques. Teams of medical personnel were enlisted to provide external compression, sometimes for days at a time, in patients with large abdominal aneurysms. Arterial walls were scarified with talc, wrapped in cellophane or filled with many meters of wire to which a galvanic current might be applied. This latter technique—aneurysmal wiring and electrocoagulation—was reported favorably as late as 1951 by Blakemore.[1] Matas of New Orleans renovated the approach of Aëtius and carried out endoaneurysmal ligature of peripheral aneurysms: such an approach is important because it spares collaterals around the aneurysm. Creech, a pupil of Matas, was later able to point out the virtues of the intrasaccular graft interposition now universally used for aortic aneurysmal repair.[2]

Interestingly, whereas peripheral aneurysms due to trauma or bacterial infection were common in the past, aneurysms of the abdominal aorta appear to be a modern disease. Osler reported seeing only one such lesion per year, similar to the incidence noted at Guy's Hospital in London in the mid-19th century.[3]

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Epidemiology

Osler would be surprised today: abdominal aortic aneurysm can be found in at least 2% of the elderly population, according to a Scandinavian postmortem study,[4] and 10% or more of the average vascular surgeon's clinical practice is comprised of patients who have abdominal aortic aneurysms.[5] Current demographic trends in Western nations, showing an ever-increasing elderly population, will undoubtedly account for an even greater increase in the number of patients with this condition.

Men outnumber women by fivefold to tenfold in susceptibility to abdominal aortic aneurysm. The vast majority of persons with abdominal aortic aneurysm are older than 60 years of age, and the median age of persons so afflicted in several large series was 70.[6] No convincing racial, environmental or geographic predilection has been noted.

Etiology

For such a common condition, surprisingly little is understood about the cause of aneurysms. They are frequently thought to be a manifestation of atherosclerosis, perhaps because of the endemic nature of this latter condition and the not infrequent concurrence of the two. It is clear, however, that aneurysms arise primarily because of deterioration in the arterial *media*. Far-advanced atherosclerosis may have both direct and indirect effects upon this layer of the artery, but it is primarily an *intimal* disease. The presentation and clinical consequences of aortic atherosclerosis are very different from those of aneurysmal disease. It has been suggested that abdominal aortic aneurysms may develop as the result of a series of structural, biochemical and hydraulic factors independent from those usually associated with the development of atherosclerosis.

With increasing age, aortic elasticity and compliance diminish, and increasing wall rigidity can be shown experimentally to cause development of a reflected wave from the aortic bifurcation. Gosling and colleagues[7] have suggested that this retrograde pressure wave causes a lateral stress on the infrarenal abdominal aorta, especially when it meets the next oncoming pulse wave. Further, Roach[8] found that turbulent flow generated distal to the branching of large tributaries, such as the renal arteries, may initiate vibrations in the arterial wall that themselves may cause medial degeneration. With deterioration of the wall's elastic lamellae, arterial wall tensile strength declines and the artery dilates in response to the intraluminal pressure, usually greater than 2.5 lbs per sq in (17.25 kPa). The aorta dilates in concert with Laplace's law ($T = P \times r$), where wall tension (T) is a function of the product of intraluminal pressure (P) and aortic radius (r). (Parenthetically, Laplace's law clarifies the role of sustained hypertension in the genesis of aneurysms.) That such hydraulic factors may play a role in the development of aneurysms seems supported by the fact that aneurysms develop throughout the body in segments of large and medium-sized arteries just proximal to bifurcations or branch points.

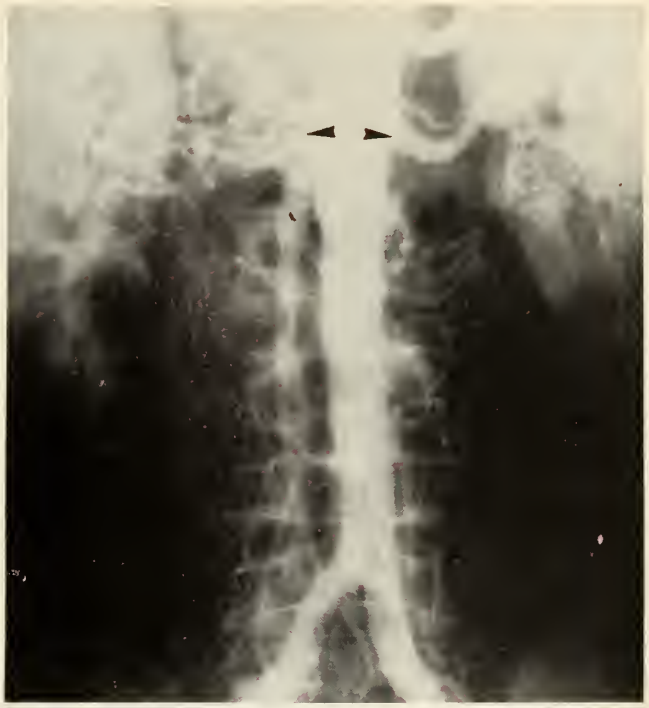

Figure 1.—A normal abdominal aortogram. Aneurysms characteristically arise between renal arteries **(arrows)** and the aortic bifurcation.

The size, shape and structure of the aorta may be germane to the development of aneurysmal degeneration. Comparative anatomic studies have shown that the human abdominal aorta may be structurally deficient in both its complement of vasa vasorum (the small arteries supplying nutrition to the outer aspects of the aortic wall) and in the number of musculoelastic units found in the media.[9] While the normal human aorta has the configuration noted in Figure 1, it frequently "uncoils" with age, becoming extremely tortuous ("ectatic"), a common finding in aneurysmal aortas (Figure 2). "Uncoiling" of the aorta may weaken its structural elements. Tilson and Dang[10] have observed that the arteries of persons with aneurysms are increased in diameter when compared with those of the normal population—a condition they call "arteriomegaly." It has also been observed that aneurysms generally arise in segments of arteries that cross joints, giving off few branches—for example, the infrarenal aorta and the popliteal artery. Repeated flexing of the artery could conceivably cause structural weakening over many decades. Thus, such uncoiled, dilated, structurally deficient and stressed segments of aorta might seem to be especially susceptible to further weakening and ballooning.

Several biochemical factors may further contribute to the pathogenesis of aneurysms. Aortic aneurysms have been shown to develop spontaneously in laboratory mice with the "blotchy" allele on the X chromosome.[11] This mutation is expressed by inhibition of

Figure 2.—Marked ectasia ("uncoiling") of the abdominal aorta, with an associated large aortic aneurysm.

the collagen-elastin bridging mediated by lysyl oxidase, a copper-containing enzyme. Interestingly, Menkes's kinky-hair syndrome, a rare sex-linked condition in newborn human infants characterized by collagen abnormalities and malabsorption of copper, may also be associated with arterial aneurysms.[12] Busuttil and co-workers[13] and Dobrin[14] have suggested that dissolution of the structural integrity of the aortic wall by collagenase may lead to aortic dilatation and subsequent rupture of aortic aneurysms. Collagenase levels are significantly higher in the walls of ruptured aneurysms when compared with unruptured abdominal aortic aneurysms or atherosclerotic aortas.[13] Adding further clinical significance to these experimental studies has been the observation[15] that patients with aortic aneurysms who undergo laparotomy (which liberates large amounts of collagenase) for other purposes may be at increased risk postoperatively for aneurysmal rupture. The possibility that a chromosomal defect, expressed as an enzymatic abnormality, leads to arterial wall deterioration lends credibility to a possible inherited tendency to form aneurysms. We are currently engaged in a population study to attempt to determine whether relatives of aneurysm patients are at excess risk of aneurysm development as well.

In short, the presence of multiple risk factors independent of those associated with atherosclerosis, as well as the relative rarity of aneurysmal degeneration in aortas severely involved with occlusive atherosclerosis, suggests that aneurysmal degeneration and atherosclerosis may be independent processes.[16]

Rare in modern experience, but worthy of mention, are the occasional aortic aneurysms that arise due to tuberculosis,[17] syphilis[18] and other bacterial infections.[19] Abdominal aortic aneurysm is also a manifestation of connective tissue disorders such as Ehlers-Danlos[18] or Marfan's[20] syndromes or pseudoxanthoma elasticum.[18] Aneurysm may occasionally develop as a consequence of aortic dissection[21] or blunt or penetrating trauma.[22]

Pathology

A normal adult infrarenal aorta measures 1.8 cm in diameter. What degree of aortic dilatation constitutes an abdominal aortic aneurysm? The literature is unclear on this question, but most would agree that an aorta is "aneurysmal" when the aortic diameter doubles —that is, exceeds 3.5 cm. In all, 95% of abdominal aortic aneurysms originate distal to the renal artery orifices and terminate proximal to the aortic bifurcation. Typically the aneurysm is a fusiform dilatation of the vessel that involves the full thickness of the wall, thereby being a "true" aneurysm. "False" aneurysms—those involving less than the three arterial layers—and aortic dissections are uncommon in this area. Turbulent blood flow within the aneurysm results in the deposition of a thick layer of fibrin, platelet aggregates and entrapped erythrocytes along the intimal surface—a so-called mural thrombus. Vessels originating from the aneurysmal portion of the aorta, such as the inferior mesenteric and lumbar arteries, may be obliterated by this coagulum. Further, the mural thrombus may fragment and ulcerate, embolizing the distal vessels, or it may thicken and occlude the aortic lumen, causing complete interruption of flow through the aorta.

The aneurysmal aortic wall exhibits progressive degeneration of the normal arterial architecture, with disruption of endothelium and necrosis of the smooth muscle cells. Calcification of the aneurysmal wall occurs frequently. The adventitia usually becomes attenuated and may fuse with nearby vital structures such as the inferior vena cava, the ureters or the gastrointestinal tract. The aortic wall may rarely thicken and become infiltrated with leukocytes, round cells and collagen, forming an "inflammatory" aneurysm, at which time the entire retroperitoneum becomes an impenetrable adherent mass.

Clinical Manifestations

Most abdominal aortic aneurysms are asymptomatic. Thus, in most circumstances they are discovered during the course of routine physical examination or diagnostic studies done for other reasons. Because the aortic bifurcation corresponds roughly with the umbilicus, abdominal aortic aneurysms are usually palpated in the epigastrium. The wall calcifications of an aneurysm may betray its presence on plain films of the abdomen obtained for other purposes. In recent years small aortic aneurysms have been more frequently noted as

an incidental finding during noninvasive imaging in patients having these studies for the evaluation of other problems.

Abdominal aortic aneurysms may be associated with diverse symptoms, depending on how the aneurysm deranges a patient's anatomy and physiology. Simple expansion of the aneurysm can compress and erode neighboring structures (duodenum, stomach, vena cava, ureter or vertebral bodies) and produce symptoms referrable to these organ systems as they are insulted. As noted, a mural thrombus is capable of embolizing distal blood vessels. Rarely, the aneurysm can itself thrombose, causing catastrophic lower body ischemia.[23] Abdominal aortic aneurysms are susceptible to infection and can present as a source of occult sepsis.[17] Chronic consumptive coagulopathy has been reported.[24]

The most dramatic and catastrophic manifestation of abdominal aortic aneurysm occurs when the attenuated arterial wall yields at last to the intraluminal pressure and the aneurysm ruptures. This is a surgical emergency over which few others can take precedence. Frequently the ruptured aorta bleeds into the retroperitoneum, and for a time the hemorrhage is tamponaded. Patients may thus have a "leaking" abdominal aortic aneurysm in which back or flank pain is the cardinal symptom. This generally progresses rapidly to the exsanguinating hemorrhage of true rupture. If the aneurysm ruptures directly into the peritoneal cavity, as it may in up to 20% of cases, the patient rapidly dies from hypovolemic shock.[25]

The diagnostic triad associated with ruptured abdominal aortic aneurysm includes back, flank or abdominal pain, the presence of a pulsatile abdominal mass and shock. Such patients should be considered to have a ruptured aneurysm until proved otherwise by laparotomy; they should be taken to the operating suite without further delay due to diagnostic studies, placement of invasive monitoring devices or attempts at resuscitation. Prolonged hypoperfusion and tissue ischemia in these elderly patients is poorly tolerated and contributes to the further complications of renal failure, myocardial infarction, stroke and intestinal ischemia.[26] The management of a patient with a ruptured abdominal aortic aneurysm is discussed in greater detail later.

A pulsatile epigastric mass is not always an abdominal aortic aneurysm: a normal-sized but ectatic aorta may be confused with an aneurysm and occasionally such a finding will turn out to be normal aortic pulsations transmitted through a large overlying neoplastic or inflammatory mass.[27] The ability to palpate a free space between the costal margin and the convexity of the aneurysm suggests limitation of the aneurysm to the infrarenal aorta, a finding first noted by DeBakey.[28]

About 10% of these patients will have associated symptoms or signs of concomitant lower extremity occlusive disease—that is, complaints of claudication or rest pain, bruits, absence of distal pulses or an abnormal ankle-arm pressure index.[29]

Just as occlusive atherosclerosis may be silently present at multiple locations throughout the arterial tree, aneurysms may also be multifocal: 4% of patients with abdominal aortic aneurysms will have an aneurysm elsewhere, and those with peripheral arterial aneurysms, such as in the popliteal or femoral arteries, have a greater than 60% probability of having a concomitant abdominal aortic aneurysm.[30]

It is important to recall that these elderly patients have a high incidence of associated chronic illness, including coronary artery disease in up to 50% and hypertension in 25%.[29,31] These conditions, as well as other afflictions of the cardiovascular system, should be aggressively sought, as their appropriate management enhances the ultimate care of these patients.

Diagnostic Studies

Investigations that may be of value in a patient with an abdominal aortic aneurysm include standard anteroposterior and lateral abdominal x-ray films, abdominal ultrasonography, computed tomography (CT) and contrast arteriography. These studies are rarely indicated in a situation wherein ruptured aneurysm is

Figure 3.—Lateral abdominal roentgenogram showing calcification in the wall of an aortic aneurysm (arrows).

a consideration, but for patients with less worrisome manifestations of aneurysmal disease, selective use allows more appropriate treatment.

The calcified media of an aortic aneurysm is visible in up to 85% of such patients on plain abdominal films (Figure 3).[32] It should be recalled that the magnification effect of standard radiographic techniques tends to overestimate aneurysmal size, such that an aortic aneurysm measuring 6 cm on abdominal x-ray film will actually measure 5 cm at operation.[33]

Contrast angiography has become a relatively safe procedure for the evaluation of patients with vascular diseases. By outlining the arterial lumen with a column of radiopaque dye, one can determine the location of vital arterial branches originating from the aorta and determine the presence of any occlusive disease. The angiogram may show an aortocaval fistula or an anomalous renal blood supply. Many surgeons believe that angiography is routinely indicated for all patients who have abdominal aortic aneurysm,[34] whereas others reserve this procedure for those in whom there is clinical suspicion of involvement of the renal arteries, symptoms or noninvasive studies suggesting lower extremity occlusive disease, or a question of compromise of the mesenteric circulation.[35] The major limitations of angiography as a screening test for abdominal aortic aneurysm are its invasive nature and the fact that a mural thrombus may fill the lumen of an aneurysm to the extent that the aneurysmal contour does not visualize. Thus, contrast angiography is not useful for diagnosing the *presence* or *size* of an abdominal aortic aneurysm, but it is helpful in planning an operation in selected patients.

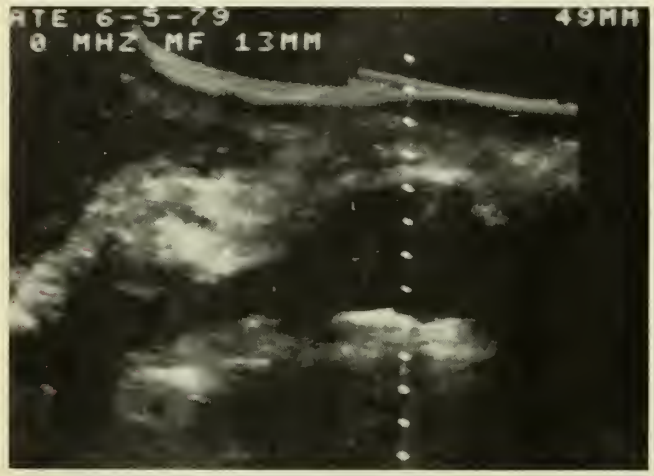

Figure 4.—B-mode abdominal ultrasonography both determines the presence of, and accurately measures, an aortic aneurysm.

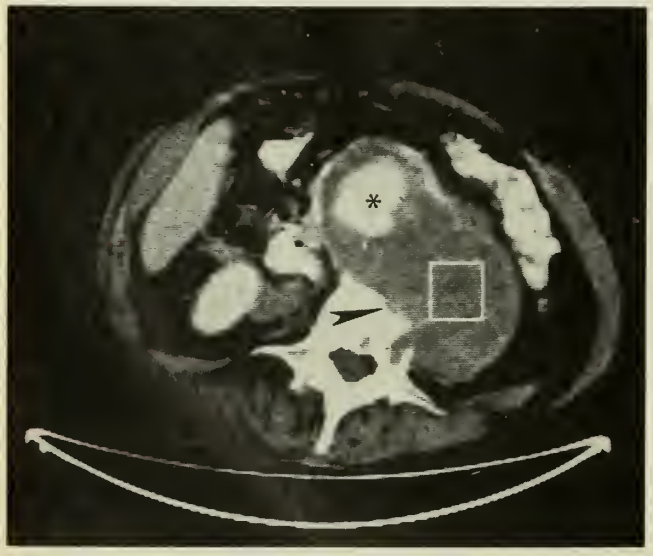

Figure 5.—Computed tomography defines a large, ruptured aortic aneurysm. Radiopaque contrast material has been administered, permitting delineation of the aortic lument (*) and its mural thrombus. Note erosion of the vertebral body by the aneurysm **(arrow).**

For routine demonstration and measurement of abdominal aneurysms, B-mode ultrasonography has the advantages of being noninvasive, painless, inexpensive, rapidly done and reproducible. It is easily done on an outpatient basis. Ultrasonography has nearly 100% sensitivity, the only difficulties being encountered in obese patients or in those with large amounts of intestinal gas.[36] B-mode ultrasonography also provides highly accurate measurements of aneurysmal dimension, essential in defining the indications for surgical intervention; it is also useful in providing serial measurements of aortic aneurysms over time in persons with equivocal indications for operation (Figure 4).[37] Finally, because aneurysms tend to occur in multiple locations, the ultrasound scan is also a good way to examine other areas in which aneurysmal degeneration is highly probable, such as the popliteal artery.[30]

Computed tomography consists of passing an x-ray source and detector array around a patient in a transverse plane, with computer-assisted generation of a cross-sectional image. The procedure may be done with intravascular contrast to provide precise definition of aortic anatomy. Multiple cross-sectional scans can delineate the aortic wall, mural thrombus and lumen for the entire length of the vessel (Figure 5).[38] Gas and fat do not interfere with the sensitivity of the study, and it is therefore useful in those patients not amenable to ultrasonography. In equivocal cases, CT is the best noninvasive method to search for evidence of aneurysmal rupture. Size estimates are highly accurate when compared with intraoperative findings.[32] The disadvantages of CT are its expense and the need for radiation exposure, both of which limit its use for screening and followup: also, CT may consume more time than is available to evaluate an unstable patient suspected of harboring a ruptured abdominal aortic aneurysm.

Review of the relative strengths and weaknesses of these diagnostic techniques suggests the following guidelines for their use:

- Patients with the classical clinical picture of ruptured abdominal aortic aneurysm require no further diagnostic studies.

• Patients who are relatively stable and in whom the diagnosis of ruptured abdominal aortic aneurysm is uncertain should be evaluated promptly by a CT scan.

• Stable persons who have abdominal aortic aneurysm in whom rupture is not a concern should be evaluated by ultrasonography to assess aortic dimensions. Many would recommend that this be followed by an angiogram if operation is planned and there is concern about suprarenal extension of the aneurysm, coincident arterial occlusive disease or the possibility of associated congenital anomalies such as horseshoe kidney, left-sided vena cava or atypical renal blood supply.

Natural History of an Untreated Asymptomatic Abdominal Aortic Aneurysm

Left unmanaged, abdominal aortic aneurysms usually enlarge, rupture and result in the death of the persons harboring them.[5,39,40] Once aneurysmal dilatation has started, immutable physical forces are in effect that, by Laplace's law, lead to progressive aneurysmal enlargement. What is the risk of rupture in a patient recently found to have abdominal aortic aneurysm?

In 1950, before the era of effective treatment of aortic aneurysms, Estes reported a study of 102 patients who had aortic aneurysms found on physical examination or abdominal x-ray film.[41] No comment was made regarding the dimensions of the aneurysms. Of the 102 patients, 60% survived for more than a year, but only 18.9% survived for five years. The survival of a synchronous age-matched population without abdominal aortic aneurysms was 80% at five years. In all, 63% of the aneurysm patients died of aneurysmal rupture. Klippel and Butcher reported similar statistics.[42]

The size of an aortic aneurysm is the single most important variable to consider in evaluating the risk of rupture. In 1955, Crane reported a 4% incidence of death due to rupture in patients with abdominal aortic aneurysms measuring less than 7 cm in diameter.[6] This finding has been confirmed in subsequent studies that have refined our appreciation of the relationship between aneurysmal size and risk of eventual rupture.[25] Contemporary thoughts about this relationship are summarized in the graph in Figure 6. We provide below our current indications for operative repair as they are affected by aneurysmal size.

Most aneurysms enlarge with time. Bernstein[43] used ultrasonography to follow a group of 49 high-risk patients with small (less than 6 cm in diameter) abdominal aortic aneurysms at three-month intervals. He reported an average growth rate of 0.4 cm per year, and proposed that a rate of growth in excess of this represents an increased risk of rupture.[37,43]

Indications for Operation

Prolongation of actuarial life expectancy, recognition of the natural history of untreated abdominal aortic aneurysms and improving resuscitative, operative and intensive care skills have resulted in a liberalization of indications for operative treatment of these aneurysms.

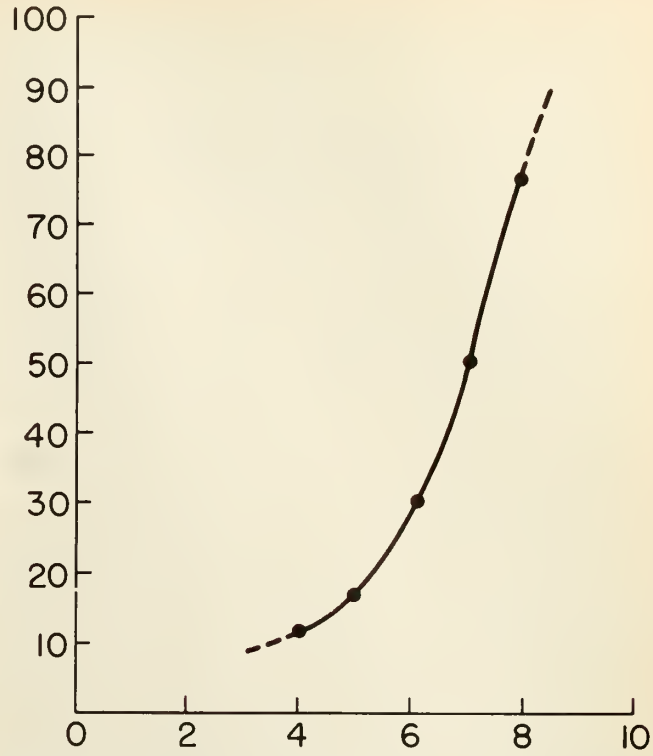

Figure 6.—Graph displaying chance of aneurysmal rupture within five years (Y axis, in percentage) as a function of diameter of aneurysm (X axis, in centimeters). (Redrawn from Rutherford.[6])

Abdominal aortic aneurysm has become a major public health concern because life expectancy in the elderly now significantly exceeds the median age, 70, at which abdominal aortic aneurysms are diagnosed.[44] Untreated, rupture of an aortic aneurysm is lethal: even when managed in expert and timely fashion, mortality may exceed 50%[40] and may be greater than 80% if rupture is accompanied by shock.[45] A patient with aneurysmal rupture always requires urgent surgical intervention, except in those situations in which the presence of a widely disseminated neoplasm or other far-advanced and debilitating chronic illness renders operative therapy a disservice to the patient.

Other complications of abdominal aortic aneurysm —compression of neighboring structures, infection and embolization—also mandate surgical correction, but generally under less urgent circumstances, allowing adequate patient preparation and some prior knowledge of possible operative pitfalls. Similarly, aortic aneurysms that are tender or that have enlarged excessively on serial ultrasonograms generally warrant repair.

Recommendations for the repair of asymptomatic abdominal aortic aneurysms have classically been formulated on the basis of aneurysmal diameter, taking into account a patient's projected life span and the presence of associated medical conditions that might influence

operative risk. Very large abdominal aortic aneurysms, measuring 10 cm or more, are occasionally discovered on routine examination. Such lesions are at exceedingly high risk for rupture, and repair of the aneurysm should be considered urgent. Smaller aneurysms permit a more deliberate approach, but patients who have abdominal aortic aneurysms measuring 5 cm or greater by ultrasonogram or CT scan should undergo elective repair unless their operative risk is very high (recent myocardial infarction or stroke; far-advanced chronic illness). Patients who have aneurysms smaller than 5 cm in diameter should also be considered for operation if they are otherwise healthy: it deserves emphasis that small aortic aneurysms *do* rupture,[46] though less predictably than large ones. *All* abdominal aortic aneurysms are at some risk of rupture, and almost invariably the aneurysm is the patient's greatest threat to life; it is a physician's responsibility to minimize this risk.

Patients who have abdominal aneurysms smaller than 5 cm in diameter, and thus are marginal operative candidates, should be educated about premonitory symptoms of rapid expansion or imminent rupture. They should be closely followed and undergo serial abdominal ultrasonograms every three to six months to seek signs of rapid dilatation. If the aneurysm appears to be expanding at a rate greater than 0.4 cm per year, then the patient may be at a higher risk of rupture and should be considered a surgical candidate.[37,43]

Other factors prompting a more aggressive approach include inflammatory aneurysms, aneurysms that are not calcified on plain abdominal x-ray film (based on the argument that a noncalcified aneurysm has grown so rapidly that its wall has not had time to calcify) and aneurysms in persons who live far from tertiary surgical care. Elective aneurysm resection can be safely eschewed in an occasionally encountered patient whose aneurysm is small and who lives with other dependable people near skilled medical care, or a person whose life expectancy is short—less than six months—due to conditions such as metastatic malignancy or severe cardiopulmonary disease. Age is not a contraindication to operation: O'Donnell reported a 4.7% operative mortality in a series of octogenarians who underwent operation for abdominal aortic aneurysm.[47]

The outcome of operation for aneurysm has improved greatly because of major advances in preoperative evaluation, blood-banking, anesthesia and postoperative care.[48,49] The average mortality reported for elective aortic aneurysm repair should be 2% to 3% in most centers.[50,51] The outcome of aneurysm repair clearly depends on the surgeon's skill and experience, and the procedure should not be done by "occasional" vascular surgeons.[52]

Treatment

An explosion of vascular techniques resulted from the pioneering research of Gross, Crafoord, Lord and others in the 1930s and 1940s. Combined with burgeoning technologies in in vitro tissue preservation and the realization that cloth and, later, plastics could be formed into substitute vessels, these advances soon led to direct attack on abdominal aortic aneurysms. Oudot replaced the infrarenal abdominal aorta for occlusive disease in early 1951, and Dubost and colleagues followed soon thereafter with excision of an abdominal aortic aneurysm and restoration of arterial continuity with an arterial homograft. A ruptured

Figure 7.—Contemporary vascular surgical technique for a large aortic aneurysm included **(left)** control of proximal and distal vessels, opening the aneurysmal sac and **(right)** suturing a prosthetic graft of appropriate dimension to the inflow and outflow vessels from within.

aneurysm was controlled, excised and replaced with homograft by Cooley and DeBakey in 1953, and Rob and co-workers used a tube fashioned out of shirt linen to replace an abdominal aortic aneurysm in 1954. In 1966 Creech[2] pointed out that the excessive morbidity and mortality, primarily resulting from blood loss, associated with aneurysm excision could be avoided by an "endoaneurysmal" approach whereby, following proximal and distal arterial control, the aortic aneurysm is opened, the adherent mural thrombus evacuated and an appropriate graft sutured to the inflow and outflow vessels from within (Figure 7). This approach, a refinement of that suggested by Aëtius 1,400 years ago, remains to the present the standard operative approach to a "routine" infrarenal aortic aneurysm. When significant occlusive or aneurysmal disease is present in the iliac vessels, a bifurcation graft to the external iliac or femoral arteries is indicated.

Specific technical issues surrounding operation for an aneurysm are beyond the scope of this discussion. Important principles, however, include the assurance of adequate vascular access, the utility of preoperative volume loading and hemodynamic monitoring,[53] typing and crossmatching of adequate amounts of blood, the value of autotransfusion devices for the administration of shed autologous blood,[54] the crucial importance of carrying out the procedure rapidly and technically correctly, prevention of "declamping shock" (a characteristic hypotension following release of aortic occlusion)[55] and vigilance against the postoperative consequences of diverse types of tissue ischemia. Occasionally, debris embolized from the aorta during manipulation of an aneurysm may lodge distally, causing lower extremity ischemia or visceral infarction.[56]

The management of a patient with a ruptured abdominal aortic aneurysm frequently taxes a hospital and its physicians to the ultimate. While such patients may present initially with only back, flank or groin pain, this is frequently but a harbinger of complete vascular collapse. Even if repair of a ruptured abdominal aortic aneurysm is technically successful, the accompanying hypovolemic shock may result in stroke, myocardial infarction, kidney failure or colon gangrene, the latter condition associated with an 80% mortality in our experience.[45]

Whereas a "symptomatic" or "leaking" aneurysm may offer, in a technical sense, few differences from a routine elective abdominal aortic aneurysm repair once the proximal aorta is controlled, a patient who suffers a ruptured aneurysm with systemic hypotension requires timely and effective resuscitation, and our experience with out-of-hospital cardiopulmonary resuscitation by trained paramedics[57] suggests that significant salvage of life may be effected by such intervention. The use of the pneumatic antishock garment as a nonpharmacologic vasoconstrictor appears to have real merit in patients with ruptured aneurysms[58]; we have successfully air-evacuated such patients up to 800 miles in this fashion.

Establishment of proximal aortic control is all-important in patients with rupture of an abdominal aortic aneurysm: this is generally obtained by clamping or compressing the infradiaphragmatic aorta through a long midline incision. Some have advocated aortic control by clamping the distal thoracic aorta through a left thoracotomy,[59] whereas Sensenig[60] has reported a technique of emergency intraluminal occlusion of the abdominal aorta by a large Fogarty catheter passed retrograde from the left brachial artery into the thoracic aorta, then carried downstream under fluoroscopic control to a proper infrarenal position.

A number of interesting and vexing lesions may present concurrently with an abdominal aortic aneurysm, thus complicating surgical management. Hardy and Timms give a good summary of several of these.[61] For example, an unusual simultaneous occurrence of horseshoe kidney and abdominal aortic aneurysm may occur,[62] potentially leading to technical problems involving preservation of renal blood flow while doing aneurysmorrhaphy. Erosion of an aortic aneurysm into nearby viscera, including the inferior vena cava[63] or the intestinal tract,[64] may occur, with a patient showing massive congestive heart failure or exsanguinating gastrointestinal hemorrhage. Development of an "inflammatory" variant of abdominal aortic aneurysm has been mentioned previously; its cause remains obscure, but the technical consequences are very clear, including intense scarring and involvement of surrounding tissues with resulting jeopardy to these structures during operative dissection. Bacterial infection of an aortic aneurysm can lead to rupture or generalized septicemia (or both),[17] and because placement of a prosthetic graft into an infected area is interdicted, aortic ligature and extra-anatomic grafting—usually axillofemoral bypass—constitute the accepted operative procedure for these patients.[65] When such aneurysms are unruptured and can be resected en bloc, we have been successful with radical aortic excision and in situ graft interposition.[66] The coexistence of other intra-abdominal disease—colon cancer, for example, or cholelithiasis—is not uncommon, and the proper timing of management, as well as the wisdom of combining aneurysm resection with operative treatment of the second condition, remains unsettled.[67]

Rarely, a patient with a very large or symptomatic aneurysm may be in too precarious a medical condition to undergo transperitoneal aneurysmorrhaphy. In such patients, Leather and co-workers[68] and Berguer and associates[69] have promoted the use of extra-anatomic bypass grafting combined with iliac artery ligature, sometimes adding angiographic transcatheter coagulation of the aneurysm using thrombotic agents or surgical glue. In these workers' hands this technique has been quite successful, though distal ligature of an aneu-

rysm may occasionally be followed by aneurysmal rupture because of increased intraluminal pressure.

Outcome

Szilagyi and colleagues[29] have shown that surgical repair of an abdominal aortic aneurysm at least doubles the survival time a patient could expect should the aneurysm remain untreated. They also noted that, in untreated patients, the most common cause of death was rupture of the aneurysm, echoing the results reported by Estes.[41] The benefits of the operation obviously do not diminish the risk of cardiac death, and myocardial infarction remains the commonest cause of subsequent demise in patients who undergo successful repair of an abdominal aortic aneurysm.[29,31] This has led, in some centers, to an aggressive search for operable coronary artery lesions in patients harboring an aneurysm.[70] DeBakey and co-workers have also demonstrated the contribution of aneurysmorrhaphy to the prolongation of life.[71]

Successful repair of an abdominal aortic aneurysm thus appears to return patients toward the normal age-matched actuarial survival curve. Operative mortality for elective aneurysmorrhaphy should be well under 5%, and in skilled hands operative mortality rates of as low as 1% to 2% are common, despite the advanced age of patients who have aneurysm. Patients undergoing urgent operation because of symptomatic aneurysm should be expected to survive at almost the same rate. Those persons whose aneurysms rupture, and whose clinical course is characterized by significant hypotension, appear to have *at best* a 50% survival—much less in circumstances in which expert prehospital resuscitation and experienced vascular surgical skills are not available.

Summary

Abdominal aortic aneurysms are common, lethal lesions that appear to arise on the basis of biochemical or structural deficiencies; these may in part be hereditary. Aneurysmal degeneration appears to be a systemic disease affecting large and medium-sized arteries, clinically significant in the infrarenal aorta in the sixth, seventh and eighth decades of life. Elective operative repair, in skilled hands, carries less than a 5% operative mortality rate, even in an octogenarian population. On the other hand, survival following operation for aneurysmal rupture is much less than 50% at most institutions. No nonoperative management has been found to arrest the inexorable progression of these lesions. Thus, because the presence of an aortic aneurysm is generally the greatest risk to a patient's survival, early elective operation is warranted in all persons who are acceptable operative candidates.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Liver Transplantation

QUESTION:

Is liver transplantation considered established medical practice or does it remain investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery and Internal Medicine, and the Committee on Organ and Tissue Transplantation, liver transplantation is considered accepted medical practice for patients carefully selected by experienced medical transplant teams in centers with the appropriate resources and commitment to support such a program.

Published reports have shown that cyclosporine is an effective immunosuppressive agent and that its use has significantly contributed to the improved survival of liver transplant patients. Since 1980 one-year survival rates have been reported as high as 70%; projections for longer term survival are promising. Individual patients have survived many years with good quality of life after transplantation.

Liver transplantation offers a reasonable therapeutic approach for some patients with end-stage liver disease who have exhausted other available medical and surgical treatment. Though liver transplantation merits broader application, as recommended by the National Institutes of Health Consensus Development Conference statement on liver transplantation, June 20-23, 1983, its full potential will be defined ultimately by continued research and coordinated evaluation. The National Institutes of Health report concludes, and this opinion concurs, that this evaluation "can best be achieved by expansion of this technology to a limited number of centers where performance of liver transplantation can be carried out under optimal conditions."

Specialty Conference

Palpable Leg Purpura and Renal Failure in a 23-Year-Old Man

Moderator
FRANCISCO P. QUISMORIO, JR, MD

Discussants
RICHARD H. BLAU, MD; MOHAMMAD AKMAL, MD, *and* MICHAEL KOSS, MD

Edited proceedings of a Rheumatology Grand Rounds Conference at the LAC-USC Medical Center, Los Angeles. Edited by Drs Quismorio and Blau.

FRANCISCO P. QUISMORIO, JR, MD:* *The medical disorders that fall into the category of "necrotizing vasculitides" comprise a heterogenous group of human diseases characterized by acute and chronic inflammatory changes in blood vessels. The pathologic process may be widespread and different caliber blood vessels in various organs may be involved. The clinical manifestations are multisystemic. Signs and symptoms such as arthritis, serositis, Raynaud's phenomenon and nephritis are features common to many of these diseases. In certain disorders, however, end-organ involvement such as pulmonary vasculitis may be the predominant clinical feature. We will discuss one of these diseases that belongs to the necrotizing vasculitides and involves predominantly skin, kidney and gut.*

Report of a Case

A 23-year-old black man was admitted to the Los Angeles County-University of Southern California (LAC-USC) Medical Center the end of June 1982 with recurrent bruising of the lower extremities. He had been in his usual state of excellent health until two weeks before admission when he noted the abrupt onset of discolorations of both lower legs. The skin lesions were reddish in color, nontender and nonpruritic. Lasting for several days, the lesions slowly resolved but then recurred. Concomitantly, he noted mild crampy and intermittent midepigastric pain that was not associated with nausea, vomiting, diarrhea or food intolerance. He also had pain of both knees and ankles without swelling. The abdominal pain and arthralgias resolved within two days. He recalled feeling feverish, but did not take his temperature. Because of the development of leg edema and persistent skin discoloration he sought medical attention.

He said he did not have chills, a prior flulike illness, sore throat, cough, alopecia, mouth or nasal ulcers, Raynaud's phenomenon, drug use or abuse or trauma.

Information regarding past medical history, social and family history and occupation was noncontributory and there was no history of allergy.

On physical examination he was well developed, well nourished and pleasant and did not appear to be in distress. The blood pressure and the oral temperature were normal. There were numerous purpuric skin lesions on his lower extremities extending up to the knees. These were 0.5 to 1 cm in diameter and in various stages of resolution, palpable and painless. Fundi on fundoscopic examination were normal. Neither the tonsils nor the pharynx was inflamed. Results of the chest, heart and abdominal examination were normal. There was 1+ pitting edema of both legs up to the midcalf. There was no evidence of synovitis in the peripheral joints, and neurologic examination showed no abnormalities.

Laboratory studies disclosed the following values:

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hemoglobin 11.1 grams per dl with a hematocrit of 35.1%; erythrocyte indices, normal; leukocyte count 8,200 per μl, with 71% polymorphonuclear leukocytes, 15% lymphocytes, 8% monocytes and 6% eosinophils; the platelet count was normal. Analysis of urine showed 2+ protein, 40 to 50 leukocytes per high-power field, 1 to 3 erythrocytes per high-power field and no casts. Blood urea nitrogen was 72 and serum creatinine 4.5 mg per dl; 24-hour urinary protein excretion was 2,000 mg and the creatinine clearance was 12 ml per minute. The serum sodium was 141, chloride 114 and bicarbonate 17 mEq per liter; calcium 9.6, phosphate 3.8 and glucose 71 mg per dl. The total protein was 8.9 grams per dl, with a serum albumin of 3.8 grams per dl. The chest x-ray examination and electrocardiogram were interpreted as normal. Cultures of urine and blood specimens were negative. A culture of a throat swab specimen grew normal bacterial flora. Antistreptolysin O titer was 84 Todd units (normal, <85) and antistreptohyaluronidase titer was 1:64 (normal, <1:128).

Serologic tests were negative for antinuclear antibodies, antibodies to double-stranded DNA, Sm antigen, nucleoprotein and rheumatoid factors. The concentration of serum cryoglobulins was 17 mg per dl (normal, <2). Serum IgG was 4,066 (normal, 600 to 2,000), IgA was 231 (normal, 50 to 400) and serum IgM was 92 mg per dl (normal, 40 to 250). Serum levels of C3 and C4 were normal. Tests for hepatitis B surface antigen and for Bence-Jones protein were negative.

Eight days following admission the patient underwent a skin and a kidney biopsy. The skin biopsy specimen showed evidence of leukoclastic vasculitis and, by direct immunofluorescence, granular deposits of IgG and IgM were found in the walls of dermal blood vessels. IgA and C3 deposits were not seen. The kidney biopsy specimen was inadequate for diagnostic evaluation.

Based on the results of the skin biopsy and evidence of active nephritis, a diagnosis of Schönlein-Henoch purpura was made. Because of progressive renal insufficiency (serum creatinine level, 6.2 mg per dl), a regimen of 80 mg of prednisone a day was begun. The skin lesions subsided completely. Renal function did not improve, but it remained stable. In mid August the patient was brought to another hospital because of abdominal pain and fever. On arrival he went into cardiac arrest and died. An autopsy was done by the Los Angeles County Medical Coroner.

Discussion

DR QUISMORIO: *Dr Blau will review the differential diagnosis and the contrasting clinical manifestations of Schönlein-Henoch purpura in pediatric and adult patients.*

RICHARD H. BLAU, MD:* This patient had the following problems: a leukoclastic cutaneous vasculitis manifested by nonthrombocytopenic palpable purpura, renal failure with nephritic syndrome, hypergammaglobulinemia, cryoglobulinemia, abdominal pain and arthralgias. Diseases known to be associated with leukoclastic vasculitis and renal failure are shown in Table 1.

TABLE 1.—*Systemic Illnesses Associated With Cutaneous Leukoclastic Vasculitis*

Systemic lupus erythematosus
Waldenstrom's macroglobulinemia
Essential cryoglobulinemia
Wegener's granulomatosis
Allergic granulomatosis
Malignant lesions: chronic lymphocytic leukemia, Hodgkin's, multiple myeloma, lymphoma
Subacute bacterial endocarditis
Rheumatoid arthritis
Hepatitis B viremia
Serum sickness
Schönlein-Henoch purpura

Systemic lupus erythematosus is known to present with vasculitic skin lesions. It is estimated that as many as 20% of patients with lupus will have cutaneous vasculitis at some time in the course of their disease.[1] Of course, systemic lupus erythematosus can cause the nephrotic syndrome with renal failure. However, serologic markers for this disorder such as antinuclear antibody anti-DNA or anti-Sm antibodies were not found.

Essential mixed cryoglobulinemia can present with these clinical signs. Features that argue against the lupus syndrome are the relatively short duration of his illness, a normal complement level and tests negative for rheumatoid factors and for hepatitis B surface antigen. In essential mixed cryoglobulinemia, the clinical course before renal failure is usually more protracted. It is associated with hypocomplementemia and about 85% of the patients show evidence of hepatitis B infection.[2]

The other syndromes or diseases shown in Table 1 do not fit the clinical presentation. The most likely clinical diagnosis is Schönlein-Henoch purpura. This syndrome consists of a triad of nonthrombocytopenic purpura, nondeforming arthritis and abdominal pain. Schönlein-Henoch purpura usually occurs in children and may be associated with other organ dysfunction.

Schönlein[3] first described the case of a patient in 1839 who had both arthritis and palpable purpura. He called the syndrome "peliosis rheumatica." Henoch[4] in 1874 reported several cases of the syndrome and focused attention on the abdominal pain, renal failure and the occurrence in children. Osler[5] in 1914 in a review of purpura coined the term "anaphylactoid purpura" because of the association of the disease with food ingestion. Gairdner in 1948 emphasized in his case reports and in a review of medical publications the increased frequency of the syndrome in children.[6] In 1970 two groups, Ballard and co-workers[7] and Cream and associates,[8] reviewed their cases of Schönlein-Henoch purpura in adults and the occurrence of renal disease. These studies have raised the question as to the difference between the adult and the childhood forms of the syndrome.

To address this, I will begin with a review of the

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TABLE 2.—*Frequency of Clinical Manifestations of Schönlein-Henoch Syndrome in Children and Adults*

Clinical Features	*Frequency of Occurrence*	
	Children Percent	*Adults Percent*
Skin lesions	100	100
Edema	75	60
Arthritis/arthralgia	60	55
Systemic involvement	80	80
Gut involvement	30-70	44
Renal abnormalities	20-30	50
Mortality	<5	14

clinical manifestations of Schönlein-Henoch purpura syndrome in children. The peak incidence of occurrence is between the ages of 4 and 11 years. The syndrome occurs in boys versus girls in a ratio of 2 to 1. Classically the disease appears after an upper respiratory tract infection in the winter. About 80% of affected children have the triad of abdominal pain, arthritis and purpura. It is estimated that renal involvement occurs in up to 50% of the children, with a spectrum ranging from proteinuria to renal failure. It is usually a self-limited disease, lasting from 6 to 16 weeks in most patients.[9,10]

The skin lesions in children appear over the buttocks and lower extremities. The rash begins as an urticarial or maculopapular lesion. Petechiae then appear that may coalesce, becoming ecchymotic or purpuric. Associated with the skin lesions is edema of the lower extremities, hands or face, which may not necessarily be related to renal failure. Biopsy of the skin lesions shows a leukoclastic vasculitis. Immunoglobulin and complement in the walls of the dermal blood vessels are frequently seen, IgA being the most common, but IgG or IgM may be present.[11]

Joint involvement occurs in as many as two thirds of children who have Schönlein-Henoch purpura.[12] The most commonly involved joints are the knees and ankles; the arthritis is nonmigratory. In adults the effusion has not been well characterized. The knees were involved in 67%, the ankles in 60%, the wrists in 28% and the elbows in 23% in one study.[8] Pain, edema and warmth may be found. X-ray films may show only soft tissue swelling.

The two most common gastrointestinal symptoms of Schönlein-Henoch purpura in children are cramping and abdominal pain. This can be such a major feature that some children have undergone exploratory laparotomy for a possible acute process in the abdomen.[13] In addition, intussusception can occur at the ileocecal valve.[14] Hemorrhage has been reported to occur and can range from occult blood in the stools to massive bleeding.[15] A protein-losing enteropathy may develop due to edema of the bowel wall.[16] Finally, bowel perforation is a rare complication.

During an acute episode, the serum IgA level is elevated. It returns to normal levels within the first few weeks after the onset of the syndrome.[17] This is one distinguishing feature between IgA nephropathy and the Schönlein-Henoch syndrome. In IgA nephropathy, serum IgA levels remain persistently elevated throughout the course of the disease.[10,17] The serum IgM level may also be acutely elevated in this syndrome. Serum concentrations of C1q, C4 and C3 are generally normal. Cryoglobulins when present contain IgA. Tests for rheumatoid factor and antinuclear antibody are negative.

Of adults who had Schönlein-Henoch purpura, 60% had some form of renal involvement.[8,18] Several studies have shown that 100% of adults with renal involvement have hematuria or proteinuria, or both.[7,8,18] Additionally, nephrotic syndrome and hematuria were found in 20% to 40% of these patients. About 40% to 50% of these patients were found to have renal insufficiency. This is in contrast to children who have Schönlein-Henoch purpura and nephritis, who only have a 22% incidence of renal insufficiency.[10]

The cause of Schönlein-Henoch purpura is not known. It has been postulated that a streptococcal infection may play an important role, as may a reaction to certain drugs such as tetracycline, diphenhydramine, aspirin and iodides. Food allergy is also suspected as a possible underlying mechanism.[19] There have been case reports of Schönlein-Henoch purpura occurring after an insect bite,[20] after exposure to cold[21] or after vaccination.[22]

The evidence for a streptococcal infection is circumstantial. The organism was identified from the throat in 24.3% of the children who have Schönlein-Henoch syndrome,[23] but only in 9.6% of adult patients.[8] However, 7.3% of control children also harbored the organism. Antistreptolysin O titers have also been studied in these patients. Both children who have this syndrome and healthy controls have a 33% prevalence of elevated antistreptolysin O titers.[24] However, half of the adults with this syndrome have elevated antistreptolysin O titers.[8] Although this was consistent with a prior streptococcal infection, it may also have represented a nonspecific elevation in serum titers.

The duration of the symptoms in both children and adults with either purpura alone or with renal failure was similar. Those with purpura had symptoms lasting as long as six months. Patients with purpura and nephritis had a more protracted course lasting as long as eight months.[8]

The frequency of organ involvement other than the skin is about equal in both groups (Table 2): 75% of children with Schönlein-Henoch syndrome have lower extremity edema, as do 60% of adult patients.[8] Arthritis occurs in 60% of the children and in 55% of the adults.[8,23] The systemic features such as purpura, gastrointestinal tract involvement, renal involvement and arthritis occur in 80% of both groups. Gastrointestinal tract involvement is the same in both, as is the frequency of renal disease. The mortality when renal involvement occurs, however, is different in the two groups. The mortality rate of adult patients with Schönlein-Henoch purpura and nephritis is 14%.[10] In contrast, the mortality rate among children with this syndrome and nephritis is less than 5%.[10]

The drug therapy for Schönlein-Henoch purpura includes anti-inflammatory agents for the arthritis. Systemic corticosteroids are often used for severe visceral involvement, such as renal disease and gastrointestinal tract symptoms. However, the beneficial effect of corticosteroids on these manifestations has not been proved. In addition, there are several reports of these patients being treated with immunosuppressive agents such as cyclophosphamide. The value of these drugs remains to be established.

In summary, Schönlein-Henoch purpura is a clinical syndrome of purpura, arthritis, abdominal pain and dysfunction of a number of organs. The adult form of this syndrome differs from the childhood form in the prognosis of the kidney disease and the morphology of the skin lesion.

DR QUISMORIO: *Dr Akmal, would you comment on the features and treatment of renal disease in Schönlein-Henoch purpura?*

MOHAMMAD AKMAL, MD:* The frequency of clinical renal manifestations associated with Schönlein-Henoch purpura varies.[8,25,26] It is mainly a disease of children with a median age of onset of 4 years, but it also occurs in adults. Males are affected considerably more frequently than females. Evidence of renal involvement is usually detected within the first four weeks of onset of the illness.[25] Occasionally repeated analyses of urine may show normal findings at the onset of illness but recurrence of the syndrome is associated with urinary abnormality.[25]

Meadow and colleagues reviewed patients who had Schönlein-Henoch purpura[25] and found that hematuria was a very common feature and nephrotic syndrome developed in about 39% of their 88 pediatric patients. The renal manifestations included nephrotic syndrome in about 30%, nephrotic syndrome with hematuria in 9% and asymptomatic proteinuria with acute nephritic syndrome in 10%. Asymptomatic proteinuria with hematuria occurred in 45% and hematuria alone in 6% of these 88 patients.

Late onset of progressive renal failure may be seen, but it is rare if it does not develop within the first three or four years following the onset of clinical symptoms.[25]

The renal manifestations are quite similar in both children and adults but the renal disease tends to be severe in adults.[8,25] Proteinuria is usually moderate or of a poorly selective type.[27]

The changes seen in renal biopsy specimens from patients with Schönlein-Henoch purpura have been classified into six histologic grades by the International Study of Kidney Disease in Children by Meadows and co-workers,[25,27,28] and are as follows:

- Grade I: Minimal glomerular abnormalities without evidence of tubular or interstitial damage.
- Grade II: Pure mesangial proliferation. At least 50% of glomeruli are normal and others show localized areas of sclerosis, hypercellularity, rare adhesions or small crescents; no tubular damage or interstitial changes.
- Grade III: a. Focal.
  b. Diffuse mesangial proliferation with less than 50% crescents.
- Grade IV: a. Focal.
  b. Diffuse mesangial proliferation with 50% to 75% crescents.
- Grade V: a. Focal.
  b. Diffuse mesangial proliferation with greater than 75% crescents.
- Grade VI: "Pseudo," membranoproliferative glomerulonephritis.

In general, nephrotic syndrome is present in a fourth of patients who have grades I, II and III and hematuria occurs in all the groups.[25,27,28] In patients with the syndrome grades II and III-a, histologic changes tend to show a better prognosis with either return of normal renal findings or persistent microscopic hematuria or proteinuria.[28] On the other hand, patients who have histologic changes of grades III-b, IV and V seem to have a worse prognosis, with proteinuria or hematuria persisting or progressing to terminal renal failure.[28]

The pathogenesis of the renal disease in Schönlein-Henoch purpura is not well defined. Preceding upper respiratory tract infections are common, with elevated antistreptolysin O titers in about 30% of patients. There is no convincing evidence, however, to link this syndrome with a group A streptococcal infection.[29,30] Similarly, despite the presence of a strong background of allergy in 25% of patients, there is no clear association of this disease with any particular allergen.[19] The demonstration of circulating IgG and IgA immune complexes, mesangial location and the granular pattern of immune deposits suggest an immune complex nephritis.[31(p283),32] The presence of IgA with late-acting complement components, including properdin, suggests activation of the alternative complement pathway.[33]

Sometimes Schönlein-Henoch purpura may be confused with poststreptococcal glomerulonephritis. Normal serum complement component and increased serum concentrations of IgA in about 50% of patients favor the former syndrome. Circulating immune complexes containing IgA and IgG are frequently found in relapse and the concentration of IgG complexes correlates with renal manifestations.[32]

In general, Schönlein-Henoch purpura is a benign self-limited disease. Meadow and associates[25] showed that 8% of their patients with this syndrome had severe renal insufficiency, dialysis or had died of renal failure, 55% were normal, 22% had normal glomerular filtration rate but urinary abnormalities and 10% had both a slowed glomerular filtration rate and abnormal urinary sediments. The poor prognostic indicators were old age, persistent proteinuria or the presence of an acute nephritic syndrome at the onset of illness.[25]

The value of drug therapy in the renal disease in Schönlein-Henoch purpura has not been well established by controlled trials. In fact, uncontrolled studies

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on the use of steroids, cytotoxic drugs, anticoagulants or intensive plasmapheresis for patients with ominous crescentic disease have had inconclusive results. Because of the favorable prognosis, frequent spontaneous remissions and the lack of a tendency for the focal lesions to progress, there is no indication for aggressive therapy for such patients.

This disease has been noted to recur in renal allografts.[34]

DR QUISMORIO: *Dr Koss will discuss the pathologic findings in the case reported here.*

MICHAEL KOSS, MD:* There was a single glomerulus present on the original renal biopsy specimen. It showed mild mesangial hypercellularity. By direct immunofluorescence microscopy, we found granular deposits of C3 in the mesangial region and small amounts of IgA, but no IgG or IgM. These findings are compatible with Berger's disease (IgA nephropathy) or Schönlein-Henoch purpura, but the paucity of tissue precludes an unequivocal diagnosis. No glomeruli were available in the electron microscopy material.

*Associate Professor, Department of Pathology, USC School of Medicine.

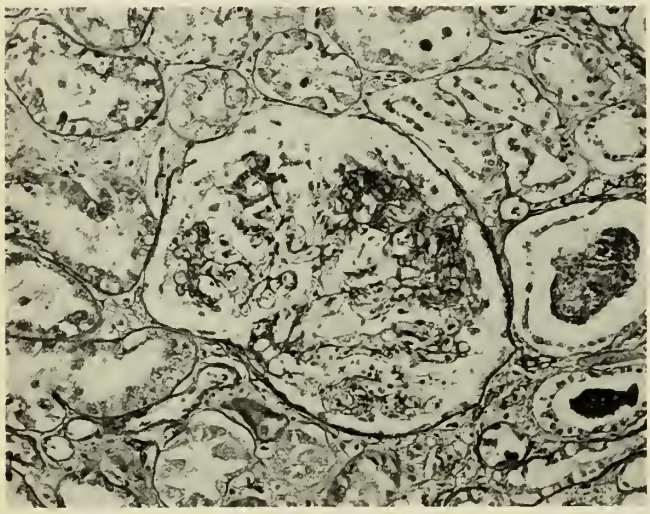

Figure 1.—A section of autopsy kidney specimen: Note the segmental area of proliferative glomerulonephritis. (Reduced from magnification ×250.)

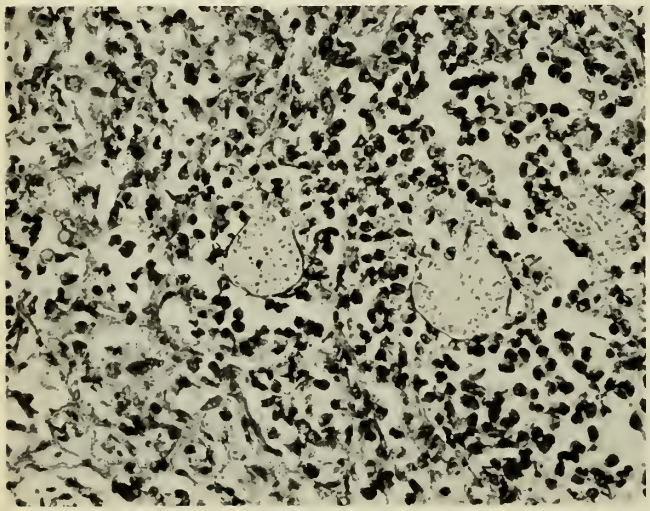

Figure 2.—A section of an autopsy specimen from the peritoneal surface of the gastrointestinal tract shows two ruptured organisms of *Coccidioides immitis* in the center of the field surrounded by acute and granulomatous inflammation. (Reduced from magnification ×630.)

The findings at autopsy were dramatic and definitive as to the cause of death, and I want to thank the Los Angeles County Coroner's office for providing us with tissue from several organs. The sections of kidney showed a severely scarred kidney. In particular, there was atrophy of the renal tubules, interstitial fibrosis and numerous obsolescent glomeruli. The viable glomeruli showed a variety of changes. While some appeared normal, others showed segmental proliferative changes or segmental glomerulosclerosis. Hence there was both focal and segmental proliferative and sclerosing glomerulonephritis (Figure 1). This type of pathologic change is consistent with that found in Schönlein-Henoch purpura.

In addition to these findings, the renal pelvis contained large stones and the patient had pathologic evidence of obstructive uropathy due to calculi with acute and chronic pyelonephritis.

Now, what was the cause of death? First of all, there was no histologic evidence of vasculitis in any of the tissues investigated, including kidney, gastrointestinal tract, liver and lung. In fact, the patient did not die of causes directly attributable to Schönlein-Henoch syndrome. Rather, there was a severe inflammatory infiltrate on the peritoneal surface of the gastrointestinal tract, consisting of suppurative and necrotizing granulomas containing the organism *Coccidioides immitis* (Figure 2). Thus, the patient died of *C immitis* peritonitis, presumably a complication of immunosuppressive therapy.

Schönlein-Henoch purpura belongs to a spectrum of renal lesions that is now believed to include benign recurrent hematuria, Berger's disease (IgA nephropathy) and Schönlein-Henoch purpura.

By light microscopy, a wide range of pathologic changes can be seen in these diseases. In benign recurrent hematuria, there may be mild mesangial cell proliferation or minimal changes. In IgA nephropathy, one can see minimal changes, mesangial cell proliferation or a focal proliferative glomerulonephritis. As Dr Akmal has pointed out, Schönlein-Henoch purpura may show any of the changes seen in IgA nephropathy, but there is a shift toward more numerous lesions and more severe ones, such as crescentic glomerulonephritis.

By immunofluorescence microscopy, benign recurrent hematuria shows, in 20% of cases, faint glomerular deposits of IgG, IgM or complement. Despite the absence of glomerular IgA deposits in benign recurrent hematuria, increased numbers of IgA-bearing lymphocytes have been found in the peripheral blood of these patients, a feature linking the disease to IgA nephropathy, which shows similar changes.[35] Granular deposits of IgA and C3 have been found in the glomerular

mesangium in both IgA nephropathy and Schönlein-Henoch purpura. However, the latter also shows variable immune deposits in glomerular capillary walls, with the degree of capillary wall involvement generally paralleling the severity of light microscopy lesions.[36] Smaller amounts of IgG, IgM and properdin have also been reported in these two diseases.

Electron microscopy of IgA nephropathy and Schönlein-Henoch purpura shows mesangial electron-dense deposits in all cases, but in this syndrome there are more extensive subendothelial deposits than in IgA nephropathy.[37,38]

In summary, Schönlein-Henoch syndrome exists as a part of a spectrum of renal diseases ranging from benign hematuria to IgA nephropathy and Schönlein-Henoch purpuric nephropathy.

Dr Quismorio: The deposits of IgA have been found not only in renal glomeruli and in dermal blood vessels, but also in blood vessels of the small intestine of Schönlein-Henoch purpura patients with gastrointestinal tract vasculitis.[39] C3 and fibrin, but not C1q or C4, have been identified in the lesion.[39] These observations have been taken to indicate an immune complex deposition process with activation of the alternative pathway of complement as a mechanism of tissue injury in the disease.

Recently, immune complexes containing IgA have been identified in serum specimens from patients with this syndrome.[40,41] Moreover, a correlation between circulating IgA immune complexes and the activity of the nephritis and the presence of IgA deposits in dermal blood vessels has been observed.[40,42] The specificity of the antibody in the immune complex and the nature of the antigen(s) have yet to be identified. Nevertheless, the presence of the circulating immune complexes has been proposed as a rationale for the use of plasmapheresis in the treatment of Schönlein-Henoch purpura.[43] Further studies are needed to establish the usefulness of plasmapheresis as a therapeutic modality for Schönlein-Henoch purpura.

Physician in the Audience: *Would we consider the* C immitis *infection etiologically significant in the pathogenesis of Schönlein-Henoch purpura in this patient?*

Dr Quismorio: While Schönlein-Henoch purpura has been reported to occur following streptococcal, mycoplasmal or viral infections, there have been no reports of cases developing after *C immitis* infection. The chronology of the events in the patient indicates that this was an opportunistic infection that developed in an immunocompromised host, eventually leading to his death.

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Medical Staff Conference

The Acquired Immune Deficiency Syndrome (AIDS)—A Multidisciplinary Enigma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR CONTE:* *Webster's dictionary defines enigma as "a riddle; a puzzle; any perplexing person or thing." The acquired immune deficiency syndrome (AIDS) is therefore, truly an enigma. What it is, where it came from, why it is occurring at this time and, above all, what causes it are unanswered questions that demand the best research effort this country can put forth. AIDS is, undoubtedly, a new disease. Its biology, mystery and impact on patients, the medical care system and society make two other new diseases—legionnaires' disease and the toxic shock syndrome—pale in comparison.*

AIDS is multidisciplinary. In Table 1 are listed only some of the medical specialties frequently consulted regarding our patients in hospital and in the outpatient clinics, or whose practitioners are interested in the patterns of disease in the community and other public health aspects of AIDS. AIDS also makes great demands on medical resources. Patients who have AIDS frequently require most—it sometimes seems all*—of the support services of a hospital.*

This discussion will be given by specialists from many of the disciplines involved in AIDS patient care and research. We will attempt to present a broad analysis of the syndrome to set the stage for a panel discussion of its many unanswered questions.

Dr Arthur Ammann will begin the discussion with a review of the immunologic aspects of AIDS.

*John E. Conte, Jr, MD, Chief, Infectious Diseases, and Associate Professor of Medicine, University of California, San Francisco, School of Medicine.

(Ammann AJ, Dritz SK, Volberding P, et al: The acquired immune deficiency syndrome [AIDS]—A multidisciplinary enigma—Medical Staff Conference, University of California, San Francisco. West J Med 1984 Jan; 140:66-81.)

Immunologic Aspects of Acquired Immune Deficiency Syndrome

DR AMMANN:† Significant immunodeficiency has been found in young homosexual men seen because of unusual disease associations.[1] It is important to emphasize that the only laboratory studies that establish a diagnosis of acquired immune deficiency syndrome are those showing abnormalities in the immune system. The combination of specific epidemiologic and clinical features and tests showing abnormal T-cell function serves to classify persons as having AIDS. As T-cell abnormalities are most prominent in persons with AIDS, groups of investigators nationwide have carried out detailed studies of T-cell immunity in various subpopulations of patients who have AIDS and related disorders. Test findings from different laboratories, using different patient populations, have resulted in agreement on the defects of T-cell immunity.[2-4] We have reported on the characteristic T-cell abnormalities found in AIDS patients who have Kaposi's sarcoma, opportunistic infection or the lymphadenopathy syndrome, healthy homosexual controls, blood transfusion-related AIDS and hemophilia-related AIDS. Most of these disorders have characteristic immunologic profiles that, in association with clinical findings and epidemiologic findings, distinguish one form of AIDS from another.[4,5]

T-Cell Immunodeficiency

The most severe form of T-cell immunodeficiency is found in patients with opportunistic infection. It is not

†Arthur J. Ammann, MD, Director of Pediatric Immunology and the Pediatric Clinical Research Center, UCSF School of Medicine.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immune deficiency syndrome
CDC = Centers for Disease Control
NIH = National Institutes of Health
UCSF = University of California, San Francisco

surprising that patients who have multiple opportunistic infection should have virtual absence of T-cell immunity. The T-cell system protects against infections from viruses, protozoa, fungi and microbial agents that are frequently found in patients with AIDS. The severe degree of immunodeficiency is reflected by a decrease in both the number and function of T cells. The total lymphocyte count and the percentage of T cells are reduced. More significantly, there is a pronounced reduction of the peripheral blood lymphocyte response to phytohemagglutinin, pokeweed mitogen and allogeneic cells (usually less than 10% of normal). The three latter assays are excellent correlates of T-cell function and the degree of T-cell deficiency seen in this group of patients is comparable to that observed in congenital immunodeficiency disorders. The extreme decrease in helper-suppressor T-cell ratios (mean of 0.4) found in AIDS patients with opportunistic infection is an additional index of severe immunologic abnormalities.

A less severe degree of T-cell immunodeficiency is observed in patients who have Kaposi's sarcoma. In both untreated and immunosuppressed patients, there is a significant decrease in T-cell function associated with depressed helper-suppressor cell ratios (mean ratio of 0.8). These abnormalities contrast to the normal helper-suppressor ratio and normal functional studies found in older heterosexual patients with traditional Kaposi's sarcoma. We have recently completed a one-year follow-up study of homosexual patients with Kaposi's sarcoma to determine if significant alterations in T-cell immunity occur. After one year, helper-suppressor cell ratios remained unchanged and the response of T cells in functional assays remained depressed.

Although not considered to have AIDS, patients who have the lymphadenopathy syndrome form a distinct group of patients with a T-cell immunologic profile consisting of depressed helper-suppressor cell ratios (mean, 1.1), depressed T-cell responses to mitogen, but normal responses to alloantigen. The less severe abnormalities of the immune system appear to correlate with the milder clinical course of these patients.

The total number of T cells and functional assays of T-cell immunity are normal in healthy homosexual controls, but the helper-suppressor cell ratios are depressed largely because of an increase in suppressor cells. Whether or not the abnormalities of the immune system found in this group of patients progress toward more severe abnormalities has not yet been determined.

Several studies have been done to determine lymphokine production in AIDS patients. Interleukin-2 is an important mediator produced by helper T cells; it has multiple biologic effects including the ability to enhance T-cell responses to mitogens and to increase T-cell cytotoxicity. A deficiency of interleukin-2 has been found in AIDS patients and the correction of several functional abnormalities can be accomplished following in vitro incubation with this agent. Clinical trials of interleukin-2 will probably begin this year.

TABLE 1.—*Medical Specialties in Research and Care of Patients With Acquired Immune Deficiency Syndrome (AIDS)*

Dermatology	Infectious Diseases
Epidemiology	Neurology
General Medicine	Oral Medicine/Surgery
General Surgery	Psychiatry
Gastroenterology	Public Health
Hematology-Oncology	Pulmonary Medicine
Immunology	Tropical Diseases

B-Cell Immunity

Early studies of cases of AIDS showed elevated immunoglobulin levels in most patients.[3,4] No typical pattern of immunoglobulin class elevation was associated with any one of the AIDS-related disorders and, in most cases, polyclonal increases in antibody were observed. These observations, associated with elevated antibody levels to a variety of viral agents, suggested that B-cell immunity was intact in patients with AIDS. We recently immunized a group of patients using pneumococcal polysaccharide and protein antigens. Patients with AIDS had lower preimmunization antibody levels and did not respond normally following immunization. Fewer than 20% of the patients had a significant increase in the antibody levels to pneumococcal polysaccharide. The paradoxic association of raised immunoglobulin levels and viral antibody levels, with an absent antibody response to newly encountered antigens, can be explained by a progressive loss of T-cell immunity or by a preemption of the immune system by B cells committed to forming antibody to viral agents. In vitro studies of B cells from patients indicate that there is unregulated immunoglobulin production.

Complement

Most studies in patients with AIDS have shown increased levels of complement and circulating immune complexes.[4,6] The composition of these complexes has not yet been elucidated, but it is likely that they are composed of antibody to specific microbial agents that chronically infect patients. These immune complexes may have secondary effects. The "idiopathic thrombocytopenic purpura" that has been described in patients with AIDS is probably a result of immune complex adherence to platelets and subsequent removal by the spleen rather than a result of autoantibody formation.

Other Immunologic Abnormalities

Natural killer cells can be detected in most persons and are thought to be a natural protective mechanism

TABLE 2.—*Acquired Immune Deficiency Syndrome (AIDS): Reported Cases by Hierarchical Risk Group as of June 20, 1983, United States**

Risk Group	*Percentage of Cases*
Homosexual or bisexual men	71
Intravenous drug abusers, no history of male homosexuality	17
Haitians, no history of male homosexuality or intravenous drug abuse	5
Hemophiliac sufferers, not Haitian, no history of homosexuality or intravenous drug abuse	1
No apparent risk factors	6

*CDC unpublished data.

against malignancy and virus-infected cells. Cytotoxicity associated with natural killer cell activity does not require prior sensitization. Decreased activity of the natural killer cells would be expected to be associated with an increased susceptibility to infection and an increased incidence of malignancy. However, studies in patients with AIDS have shown variable degrees of natural killer cell activity, ranging from depressed to increased. Decreased lymphocyte cytotoxicity directed toward cytomegalovirus-infected cells has been a more consistently abnormal finding.

Immunologic Evaluation of a Patient Suspected of Having AIDS

The immunologic evaluation of a patient suspected of having AIDS is essential. The degree of immunodeficiency is predictive of prognosis and may determine specific diagnostic and therapeutic approaches. Abnormalities of the T-cell system must be present before a patient with appropriate epidemiologic and clinical features can be considered to have AIDS. The degree of abnormality correlates well with clinical findings and susceptibility to malignancy as well as opportunistic infection. Patients with significant degrees of T-cell immunodeficiency should be given trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis carinii* and should have all blood products irradiated to prevent lethal graft-versus-host disease. Studies of the immune system will assist in determining progression of the disease and the effectiveness of established and experimental therapy in reversing the acquired immunodeficiency.

Acquired Immune Deficiency Syndrome—Epidemiology

DR DRITZ:* The Centers for Disease Control (CDC) have defined the acquired immune deficiency syndrome as a "reliably diagnosed disease that is at least moderately indicative of an underlying cellular immunodeficiency in a person who has no known underlying cause of cellular immunodeficiency nor any other cause of reduced resistance reported to be associated with that disease." (The Case Definition of AIDS Used by CDC for Epidemiologic Surveillance, March 15, 1983; unpublished report circulated to local health officers and other health professionals). The basic pathologic feature is a dysregulation in the composition and function of units of the immune system. Superimposed on this basic immune dysfunction are biopsy-proved malignant tumors—that is, Kaposi's sarcoma and diffuse undifferentiated non-Hodgkin's lymphoma—or rare opportunistic infections that are not seen in persons with normally functioning immune systems—that is, *Pneumocystis carinii* pneumonia, cryptococcal meningitis and atypical mycobacteriosis. The malignant lesions and opportunistic infections may occur separately or in combinations. Cases that meet these criteria are designated by the CDC as AIDS-category A1. In a second group of possible acquired immune deficiency conditions, the most frequently seen is the lymphadenopathy syndrome, which may be a prodromal phase of AIDS-A1 or a milder form of AIDS, or a corollary condition that can develop in the same population groups as does AIDS-A1. How much more potential AIDS disease now exists is impossible to determine, but we may be seeing only the tip of the iceberg.

Five cases of *Pneumocystis* pneumonia in men without a known predisposing illness were reported in southern California in 1981. By June of 1983, the CDC had recorded 1,676 cases of AIDS in 39 states, the District of Columbia and Puerto Rico, with an overall mortality of 39%; 118 cases were recorded in 20 other countries. Among the US cases, 71% were recorded in homosexual or bisexual men, 17% in heterosexual male and female intravenous drug abusers, 5% in recent Haitian entrants to the United States of both sexes, 1% in persons with hemophilia and 6% in persons who have no known risk factors; half of the latter, however, have either no history or inadequate medical histories available (Table 2).[7] The number of cases has risen logarithmically and the varieties of complicating opportunistic infections have multiplied. At the last report from CDC, cases were still doubling in number every six months. The only hopeful break in this progression is in a report in June 1983 from Dr David Sencer of the New York City Health Department that reports in his area seem now to be slowing down. Dr Andrew Moss and his epidemiology group at the University of California, San Francisco (UCSF), have analyzed some of the case data at the San Francisco Department of Public Health and developed incidence curves that show a logarithmic rise that almost exactly parallels the New York curve, but with a one-year delay (Figure 1). Therefore, we hope that the New York downtrend (if it persists) will be mirrored in the San Francisco Bay Area in the coming year. CDC case reports from other cities between the two coasts seem to follow a similar pattern—again, one year behind the Bay Area.

In late 1981, the San Francisco Department of Public Health participated in a CDC-directed case-control study of risk factors for AIDS in a sample of 50 homo-

*Selma K. Dritz, MD, Department of Public Health, City and County of San Francisco.

sexual and bisexual men with AIDS and 120 matched healthy homosexual controls. Reported by Jaffee and his group at CDC, the patient profile defined a gay or bisexual man with mean age of 33 years, with 16 years of schooling and $20,000 or more annual income. Among major risk factors in the cases were a history of multiple and repeated infections with both classic and enteric sexually transmitted diseases, and a history of multiple and diverse sexual encounters. Of major significance among the infections were syphilis, non-B hepatitis and acute amebiasis. Radically different from the sexual history of the control group, which reported a mean of 25 sexual partners in the previous year, was the mean of 65 different sexual partners of men with AIDS in the year before onset of their symptoms, with 50% or more of those partners encountered in the anonymous setting of gay bathhouses. The intravenous abuse of drugs was a less clear risk factor in cases involving homosexual men, as only 12% of those on the East Coast and none of those in the Bay Area admitted using drugs intravenously, compared with nearly 60% users among cases involving heterosexual men and women.[8,9]

Lacking clear identification of an etiologic agent, we are reduced to using our epidemiologic data to develop theories of the cause of AIDS. Some of the findings strongly suggest a transmissible biologic agent as the cause of the primary immunosuppression, with the cytomegalovirus or some mutant form of it heading the list. However, even when cytomegalovirus is identified in tissues of patients, it is not yet possible to determine whether or not it is the primary causative agent because it may be merely expressed from a prior latent stage after immunosuppression of the host by some other still unidentified mechanism. A cytomegalovirus is considered a major candidate because it has been related to the classic forms of Kaposi's sarcoma seen in Africa and the eastern Mediterranean littoral. The current epidemic form resembles the classic variety only under the microscope, however, suggesting the possibility of a mutant form of the virus. Reported also, by Drew and co-workers in San Francisco, is a significantly higher antibody prevalence in a sample of healthy homosexual men they studied, as compared with control groups of healthy heterosexual men.[10]

Other candidate viruses include the human T-cell leukemia virus found in 30% of AIDS cases tested recently, though AIDS is not reported from those areas in Japan that are major loci for human T-cell leukemia virus prevalence. Other suggestions include the African swine fever virus, reported from Kaposi's sarcoma areas in Africa and Haiti, and additional "viruses of the week." Recent entrants from Haiti who have AIDS have denied both homosexuality and the intravenous use of recreational drugs, but a recent single report suggests that the histories may not be entirely accurate. In addition to viruses, the theories of cause include a possible genetic variant (an HLA-DR5 locus is proposed by Friedman-Kien in New York) and immunologic overload with exhaustion of the immune system

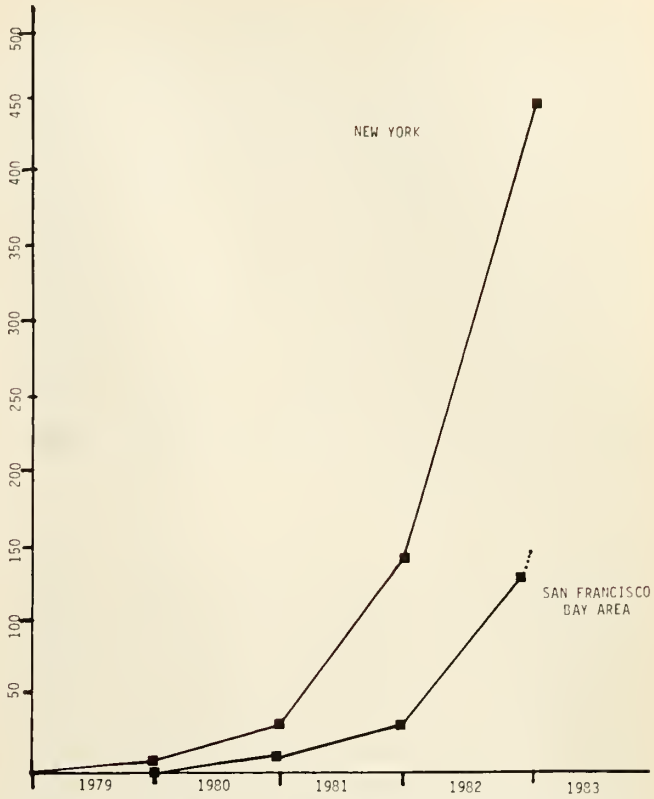

Figure 1.—Cumulative number of acquired immune deficiency syndrome (AIDS) cases by onset year, New York and San Francisco, 1979 through 1982.

from a rapid succession of a multitude of infections, as reported in the medical histories of most of the AIDS patients. A host of chemical agents has also been proposed, including both orally and intravenously taken recreational drugs, chemicals used as sexual stimulants and the steroids now popularly used as an adjunct to body-building regimens.

Transmission

Two major means of transmission have been suggested for the infectious agent. One is sexual transmission based on the major risk factor identified in the case-control study, which involves multiple sexual contacts using vigorous or traumatic anogenital or digital techniques ("fisting," for example), tearing or abrading the anal or rectal mucosa and opening small blood vessels. Darrow, reporting for the CDC, found a cluster of cases in Los Angeles, a finding that strongly supports a theory of a sexually transmitted agent with a probable incubation period of 7 to 24 months.[11] We have several similar clusters in the Bay Area, and plan a control study to test the significance of these clusters vis-à-vis the frequent and intimate contacts of sexually active gay men in the concentrated milieu of the "fast lane."

Blood transfusion is the second avenue of infections proposed, either for blood or specialized blood products, such as the factor VIII used in the treatment of hemophilia. The CDC reports ten cases of probable

AIDS in blood recipients in a total of 10 million transfusions. In San Francisco, what appears to be AIDS developed in an infant, a patient of Dr Ammann, about five months after the infant was given multiple transfusions at birth, one of which was from a donor in whom clear AIDS developed seven months after the donation. Both subsequently died and studies are in progress.[12] Reports of cases of AIDS in 14 patients with hemophilia and in heterosexual intravenous drug abusers bolster the theory of blood transmission as a mechanism of infection with AIDS. The difficult question of identifying AIDS high-risk blood and donors is under intensive study. Vertical transmission is also postulated in 15 small children with apparent AIDS whose mothers have AIDS, are intravenous drug abusers, are Haitians or are sexual consorts of men who have those risk factors.

Mortality

Finally, I want to focus on AIDS mortality, which is far higher than the 25% recorded in some historic smallpox epidemics. Bald numbers do not adequately indicate the gravity of this outbreak. The CDC reports overall mortality to date of about 40%, but 80% by two years after diagnosis and almost 100% by three years. According to a recent indirect report from Dr Linda Laubenstein in New York, some improvement in survival times was found in those of her patients with Kaposi's sarcoma in whom other opportunistic infections did not develop. In curves prepared by Moss and his group at UCSF from 170 case histories in our files at the San Francisco Department of Public Health, the picture is grim: only 50% survivors of Kaposi's sarcoma by 21 months after diagnosis, no survivors of opportunistic infections by 21 months and no survivors of both Kaposi's sarcoma and opportunistic infections by 15 months after diagnosis. The curves are no more hopeful if we compare cases diagnosed early—before 1982—with more recent ones, who came to medical attention and who started therapy earlier in the course of their disease.

We will need more work, by more people, and more time to conquer the puzzles of this syndrome. And TIME is what the patients do not have.

Malignant and Hematologic Manifestations of the Acquired Immune Deficiency Syndrome

Dr Volberding:* The existence of the acquired immune deficiency syndrome was first appreciated because its major manifestations include diseases that before this epidemic were distinctly unusual in the patient population affected. Specifically, these manifestations have included unusual malignant disease and opportunistic infections. Had AIDS been associated with more common diseases, it is doubtful that we would be as aware of this epidemic as we are today. While hematologic disturbances are not at all uncommon with AIDS, certainly the major features of clinical importance have been infectious and malignant diseases. In this review I will discuss the major malignant characteristics of AIDS, with particular emphasis on the most common cancer seen in this disorder, Kaposi's sarcoma. I will highlight some of the clinical features of this malignancy, the various features of its natural course and the results of therapeutic trials.

The presence of a system of immune surveillance in humans has been postulated for a number of years.[13] According to this theory, malignant cells arise as a chance event in the process of cell division but are recognized and eliminated as a result of the system of cellular immunity. Whereas the precise mechanisms of this surveillance have not been elucidated, major functions are felt to be associated with macrophages and cytotoxic lymphocytes. This theory has been attractive and has been, in part, supported by studies in other hosts but direct confirmation of active immune surveillance in humans has been difficult.

Although direct proof of immune surveillance is lacking, substantial circumstantial evidence supports its existence. Primary among the tumors considered due to defects in this system are the types of cancer associated with AIDS. Specifically, they include Kaposi's sarcoma and lymphoreticular neoplasms.

Before AIDS, Kaposi's sarcoma affected three principal populations: elderly men—especially of Italian or Jewish ancestry, black equatorial Africans and patients with iatrogenic immune deficiency. We have learned a great deal about the treatment of Kaposi's sarcoma in AIDS from the second group, but it is the third group of Kaposi's sarcoma patients who are likely to yield the most significant information about the cause of Kaposi's sarcoma in AIDS. As such, this group warrants close scrutiny. The occurrence of malignant disease following renal transplantation has been appreciated and reported for more than ten years.[14] Lymphoreticular neoplasms have been seen, but the most common malignancy following renal transplantation has been Kaposi's sarcoma.[15-17] Typically, Kaposi's sarcoma has been diagnosed from 9 to 16 months following renal transplantation, and has followed a clinical course not unlike that seen in the acquired immune deficiency syndrome. While Kaposi's sarcoma in elderly men is typically an indolent disease initially confined to the skin of the feet and lower extremities, Kaposi's sarcoma seen with renal transplantation often disseminates early in its course and rapidly progresses in the absence of appropriate therapy. Chemotherapy and radiation therapy have both been used for the Kaposi's sarcoma associated with renal transplantation, but the number of cases treated has not been sufficiently large to draw any firm conclusions. One of the most common approaches to the treatment of renal transplant-associated Kaposi's sarcoma has been to discontinue giving immunosuppressive medication in the hope that restoration of immune competence would result in tumor control. In fact, this has been done in most cases reported in the literature and has resulted in impressive responses in nearly half of the cases.[17] While

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administration of immunosuppressive drugs has often been discontinued in conjunction with other forms of therapy, it appears that withdrawing prednisone and azathioprine alone can result, at least in some cases, in tumor remission. As such, the renal transplant-associated Kaposi's sarcoma may provide important insights into the management of current cases of this cancer in AIDS.

Another group important in our understanding of the natural history and treatment of Kaposi's sarcoma are those cases occurring in equatorial Africa. There Kaposi's is an endemic disease and in some areas is the most common form of malignancy.[18] Unlike classical forms of this tumor seen in elderly men of Mediterranean and Jewish descent, cases of Kaposi's sarcoma in Africa are often widespread and follow an aggressive course.[19] This is especially true of younger patients with lymphadenopathic varieties of the disease. Minimal information has been accumulated on the treatment of traditional forms of the tumor in the elderly, but a number of clinical trials have been carried out regarding African varieties of Kaposi's sarcoma, particularly at the Uganda Cancer Institute. In Africa, a number of drugs have been used as therapy for Kaposi's sarcoma that appear to have a substantial objective response rate, including some agents with response rates of over 80% (John L. Ziegler, MD, UCSF, oral communication, June 1983). Certainly, the most important difference between the cases of Kaposi's sarcoma in Africans and in those with AIDS is the apparent lack of underlying immune deficiencies in the African patients. Therefore, the types of opportunistic infections commonly seen in AIDS were not seen in Africa as underlying problems or as complications of therapy. Nevertheless, when approaching chemotherapy trials of AIDS-related Kaposi's sarcoma, the experience with treatment in Africa may help in selecting agents to receive initial testing.

Therapy for Kaposi's Sarcoma in AIDS

Given the difficulties outlined above and the many novel features of Kaposi's sarcoma in cases of AIDS, it should not be surprising that some problems have been encountered in designing appropriate therapeutic trials for this new disease. Much of the early work has been based in part on recommendations of a 1981 National Institutes of Health (NIH) workshop on the treatment of Kaposi's sarcoma.[20] Members of this workshop recommended treatment approaches based on prior experience with the African form of the disease. Specifically, a preliminary staging system was proposed that divided patients with Kaposi's sarcoma in AIDS into groups of indolent or aggressive progression of disease, and limited or extensive tumor dissemination. The panel recommended that patients with limited disease be treated with radiation therapy and that patients with widespread disease be treated with chemotherapy. Single agent therapy was recommended for those patients with slower disease progression, whereas combinations of drugs were recommended for patients with more rapid progression of the disease.

Initial approaches to the treatment of Kaposi's sarcoma in AIDS, based on the NIH panel recommendations, have included work especially at New York University (NYU) and UCSF. Investigators at NYU have treated patients who had earlier stage disease with single agent VP-16-213 (code designation for etoposide, a podophyllotoxin), and patients who had more advanced disease with the combination of doxorubicin hydrochloride (adriamycin), bleomycin and vinblastine sulfate. Similarly, patients at UCSF are treated with vinblastine if their disease is more limited or slowly progressing in nature, whereas patients with more aggressive courses are selected for treatment with the combination of doxorubicin, bleomycin and vinblastine.

The experience with VP-16-213 has been very promising. A response rate of about 80% has been reported, with nearly half of these responses being complete tumor remissions.[21] Perhaps because of selection criteria (patients with preexisting fever, weight loss or night sweats were excluded from this therapy), the incidence of opportunistic infections seen with VP-16-213 therapy has been relatively low. To date, in only 12% of treated patients have serious opportunistic infections been reported to develop while they were receiving VP-16-213 therapy.[21] The toxicity of this drug is modest, primary side effects being confined to bone marrow where moderate myelosuppression has been observed. If confirmed by other investigators, the results seen with VP-16-213 are indeed impressive and this drug could become a mainstay of therapy for Kaposi's sarcoma.

Vinblastine is the other single agent that has been tested extensively in AIDS-associated Kaposi's sarcoma. This drug, a *Vinca* alkaloid, has even more acceptable toxicity than VP-16-213, causing no significant alopecia or nausea. Its major toxic effect, again, is myelosuppression.[22] In AIDS-associated Kaposi's sarcoma, vinblastine has had a definite effect, though probably not as substantial as VP-16-213. In our study of 22 patients, objective partial or complete remission was achieved in 37%.[22] The duration of this remission has been longer than eight months. Unlike the studies using VP-16-213, this trial of vinblastine included patients with preexisting fevers, night sweats or weight loss, and the incidence of opportunistic infections in treated patients was 22%. While it does not appear to be adequately effective as a single agent in Kaposi's sarcoma associated with AIDS, vinblastine will probably continue to serve a useful role as a component of combination therapies.

Experiences at several major institutions with combination chemotherapy using doxorubicin, bleomycin and vinblastine have been strikingly similar. An objective response rate of 50% to 80% has been observed but the rate of opportunistic infections is also extremely high. Opportunistic infection rates of more than 50% in patients treated with the combination of drugs are reported.[22] While it is difficult to determine

the reason for this high incidence of opportunistic infection, it most likely represents either the inclusion of patients with occult infections at the time of therapy initiation, or that the treatment itself may be additionally immunosuppressing, thus making their patients more susceptible to these life-threatening infections. If the latter is the case, combination chemotherapy may be of no benefit in prolonging survival and may even in some cases be detrimental.

Interferon Therapy

Because of problems seen with chemotherapy, especially the high rate of opportunistic infections, and because of the novel underlying immunodeficiency in AIDS-associated Kaposi's sarcoma, approaches other than the use of standard chemotherapeutic agents have been investigated. Chief among these have been trials of α-interferon. These trials have been based on the three postulated mechanisms of action of interferon, namely, its antiviral, immunomodulating and antineoplastic capabilities. Because of the postulated viral cause and frequent associated opportunistic viral infections, and because of the underlying immune deficiency and rapid progression of tumor in many patients, this approach appears to be warranted.

The initial trial of α-interferon therapy for Kaposi's sarcoma was conducted in New York at Memorial Sloan-Kettering Cancer Center. In this trial, recombinant α-interferon was administered to patients in a dose of 36 million to 54 million units per sq m of body surface area intramuscularly on a daily basis. With this therapy, an objective (complete and partial) response rate of 38% has been noted in patients with advanced disease. The toxicity of interferon in this trial was primarily subjective, with many patients complaining of fever, chills and a general flulike syndrome. In this study there was the suggestion that some immunologic variables, particularly the helper-suppressor T-cell ratio, might be augmented by the therapy used.[23]

The second major trial of interferon in Kaposi's sarcoma in AIDS has been conducted jointly by investigators at the University of California at San Francisco and at Los Angeles.[24] In this trial, 20 patients were randomly selected to receive either a low or a high dose of a recombinant α-interferon. The low-dose patients received 1 million units per sq m of body surface subcutaneously, while the high-dose patients received 50 million units per sq m, intravenously. Both groups were treated each day for five consecutive days on alternate weeks for a two-month induction period, followed by a lower dose maintenance phase in the high-dose group. Patients failing to respond to either regimen were offered the option of crossing over to the other. In this trial, an objective partial response rate occurred in three patients treated with the low-dose regimen and in five patients treated with the high-dose regimen. Responses have been durable with a median follow-up time of eight months, and all responding patients are still alive. The toxic effects of α-interferon in this trial were again primarily subjective and most notable in those patients receiving high-dose therapy. In this group, fever, chills, fatigue, malaise and headaches were common, being seen in essentially all patients. Objective toxic effects included modest neutropenia and slight elevations in amino transferase levels. Only one patient was dropped from the study because of a subjective toxic reaction. The rate of opportunistic infections in treated patients has been comparable to that seen with single agent chemotherapy. In only two patients did an opportunistic infection develop while they were receiving interferon therapy; six additional patients have become infected two to three months after discontinuation of this treatment.

Radiation Therapy

The use of radiation therapy in Kaposi's sarcoma unassociated with AIDS has been limited, and no reports on its controlled use in the current epidemic are available. Anecdotally, several patients have received palliative radiation therapy for painful or cosmetically disfiguring lesions. In these patients, Kaposi's sarcoma in AIDS appears to be a very radioresponsive tumor with often dramatic tumor regressions seen with doses as low as 2,500 rads (Ruth H. Grobstein, MD, UCSF, oral communication, June 1983). While additional studies are clearly needed and should be carried out in a more controlled fashion, it is likely that irradiation will have a continuing role in the treatment of this disease.

Prospects for Further Therapy Trials

In the treatment of Kaposi's sarcoma in AIDS, it is important to remember that the true underlying disease in these patients is not a malignancy but an immune deficiency. Until this immune deficiency can be corrected, it is unlikely that the therapy for the malignant manifestation of the disease will substantially change an individual patient's prognosis. Because of this, it is extremely important that the precise pathogenesis of the immunologic defect be elucidated. Until this has been done, it is unlikely that any therapy will reverse this underlying defect. Meanwhile, further trials will be needed to investigate both additional chemotherapeutic agents and immunomodulating agents. In the first group, sequential single agent testing of drugs found effective in African Kaposi's sarcoma or in similar tumors in the United States should be done. In this way, we may hope to develop a more rational approach to the use of multiple drug therapies. Also, during this testing, we may hope to learn more about the natural history of this disease and validate a clinically relevant staging system. Biologic response modifiers to be tested in AIDS-associated Kaposi's sarcoma will include other interferons such as recombinant γ-interferon and other biologic agents such as interleukin-2. Although interesting and potentially valuable, these agents are unlikely to correct the underlying immune deficiency permanently. A potentially curative approach to therapy for AIDS that is being actively investigated is the use of bone marrow transplantation.

TABLE 3.—*Infectious Agents Associated with Acquired Immune Deficiency Syndrome (AIDS)*

Viruses	*Bacteria*	*Protozoa*
Cytomegalovirus	*Chlamydia trachomatis*	Cryptosporidium
Adenovirus	*Nocardia asteroides*	*Toxoplasma gondii*
Varicella-zoster	*Salmonella* sps	*Pneumocystis carinii*
Herpes simplex virus 2	*Legionella pneumophila*	
Epstein-Barr	*?Listeria monocytogenes*	
Fungi	*Mycobacteria*	*Helminths*
Cryptococcus neoformans	*Mycobacterium avium-intracellulare*	*Strongyloides stercoralis*
Candida sps	*Mycobacterium tuberculosis*	

Two unconditioned identical twin transplants have been carried out by investigators at the University of California, at San Francisco, and at Los Angeles, with no evidence of benefit. Additionally, one identical twin pair is being transplanted after preconditioning with irradiation and chemotherapy. While no positive results are yet reported, it is hoped that transplantation from identical twins may result in a reconstitution of immune function in the patient who has AIDS, assuming that the transplanted marrow is not infected with an AIDS agent.

Conclusion

In this discussion, I have reviewed the major malignant manifestation of AIDS, Kaposi's sarcoma. It is understood that other tumors, such as central nervous system lymphomas or other undifferentiated lymphomas and carcinomas, may arise as a result of a deficiency in cellular immune response.[25] It is also appreciated that hematologic manifestations of AIDS are extremely common and that some, such as thrombocytopenia, may be extremely important clinical problems.[26] While the work done in investigating the treatment of Kaposi's sarcoma in AIDS has been rewarding, many questions remain to be answered. These include (1) the natural history of the malignancy, (2) appropriate staging of the disease, (3) the role of chemotherapy in the treatment of Kaposi's sarcoma and (4) prospects for immune reconstitution. Given the tremendous interest in this disease and the active research being conducted into its etiology and pathogenesis, these answers should be forthcoming.

Opportunistic Infections in AIDS

DR FOLLANSBEE:* The subject of opportunistic infections in AIDS needs little introduction, for the mortality of this complication of AIDS has already been pointed out. In early reports it has been noted that persons with AIDS are at risk for multiple concurrent or sequential infections.[1,27-29] For instance, it is not uncommon to treat a patient for *Pneumocystis* pneumonia, esophageal candidiasis and severe perianal herpetic ulcerations, find cytomegalovirus in an initial lung biopsy specimen and grow *Mycobacterium avium-intracellulare* from the same specimen.

The organisms reported as opportunistic in the setting of the profound immunocompromise of AIDS represent every major group of the microbial kingdom (Table 3). These infections cannot all be covered in depth. Rather, in this discussion I will introduce the spectrum of infectious complications, point out difficulties in diagnosis and describe the treatment modalities that are available and their limitations. There is undoubtedly much more to be done.

These are not new infections. Each organism has been recognized as a cause of self-limited illness or as an opportunist in humans. *P carinii* was recognized in the United States in 1955 as the cause of interstitial plasma cell pneumonia in malnourished and protein-deficient infants.[30] The risk of pneumonia from this protozoan has been well recognized in immunosuppressed persons before AIDS. Now it is seen in about 50% of all AIDS patients.

M avium-intracellulare has been recognized as a harmless respiratory tract colonizer or, less frequently, as a respiratory tract opportunist[31] in patients with intrinsic lung disease, including pulmonary emphysema, severe chronic obstructive pulmonary disease and various forms of pneumoconiosis. It has rarely been recognized as a cause of disseminated disease until the epidemic of AIDS.

Toxoplasma gondii is well recognized to cause congenital defects as well as encephalitis, myocarditis and pneumonitis in immunocompromised persons.[32] About 10% of AIDS patients have central nervous system disease, and half of these are attributable to acute toxoplasmosis.[33]

Coccidia, including *Isospora belli* and *Cryptosporidium,* have been well recognized as the cause of disease in a number of animal species and an unusual cause of a self-limited diarrheal illness in immunocompetent adults.[34] It is a true zoonosis. The illness is so often recognized in AIDS, producing between 6 and 25 bowel movements a day with volumes estimated from 1 to 17 liters,[35] that most clinical parasitology laboratories in the San Francisco Bay Area have developed procedures for the rapid diagnosis of this protozoan from stool specimens.

The histopathologic findings in these diseases tend to be overwhelming and represent one of the more

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TABLE 4.—*Differential Diagnosis in Acquired Immune Deficiency Syndrome (AIDS)*

Pulmonary Disease	*Diarrhea or Colitis*
Pneumocystis carinii pneumonia	Cytomegalovirus
Mycobacteria	Cryptosporidiosis
Typical	Fungal
Atypical	Atypical mycobacteria
Adenovirus	"Unusual" pathogens— *Salmonella, Shigella, Campylobacter, Entamoeba histolytica*
Cryptococcus and other fungi	Kaposi's sarcoma
Legionella	Unknown
? Chlamydia	
Nocardia	
Kaposi's sarcoma	

dramatic features of these illnesses. For example, mycobacterial disease in AIDS is rarely associated with classical caseating granuloma.[36] Instead, it has the pathologic appearance of lepromatous leprosy.[37] Biopsy specimens show very poorly defined collections of large macrophages with pale, foamy cytoplasm packed with acid-fast bacilli. In immunocompetent persons the initiation of the granulomatous response is thought to require an intact, antigen-specific T lymphocyte, probably of the helper-inducer subset. It is not surprising that granulomata are not seen in patients with AIDS, who uniformly have a profound depletion of the helper-inducer lymphocyte population. Lung tissue often shows on silver methenamine stain overwhelming numbers of *Pneumocystis* organisms in the alveoli. One patient seen with cryptococcal meningitis had a lymph node whose architecture was totally destroyed by organisms. This points out that indications for special stains and cultures cannot rely on the appearance of a classical histologic response but must be anticipated from the clinical presentation.

The presenting symptoms may be general and nonspecific or referable to the organ system involved. The severity of complaints may be quite variable. The clinical presentation is complicated by the fact that members of the population groups at identified risk for the acquisition of AIDS are still susceptible to the multitude of common pathogens that infect immunocompetent persons. It is often the duration of symptoms and their poor response to empiric therapy for these more common conditions that dictate the need for further evaluation. In addition, prodromal characteristics such as weeks to months of low-grade fevers, unintentional weight loss, malaise, night sweats, nonspecific diarrhea and loss of libido may alert a clinician to the possibility of an immunodeficiency state and an opportunistic infection. A history of recurrent thrush, varicella-zoster or prolonged episodes of folliculitis slowly responsive to standard therapy may be additional symptoms of a depressed immune system. Findings on physical examination often confirm the history. In addition, diffuse and nontender adenopathy is seen in about 25% of patients with opportunistic infections.

Evaluation of these symptoms may be very extensive. Protocols for these evaluations are still undergoing development. For example, patients with *P carinii* or other opportunistic pulmonary infections often have a nonproductive cough, mild to pronounced exertional dyspnea and shortness of breath, as well as worsening fevers with night sweats. Arterial hypoxemia on room air is often documented out of proportion to a patient's age or smoking history. Many patients are noted to have lymphopenia and an elevated erythrocyte sedimentation rate. However, none of these is a sine qua non and *Pneumocystis* pneumonia has been seen in patients with no fevers and only a mild exertional cough and dyspnea. The necessity for further diagnostic evaluation to rule out *Pneumocystis* pneumonia or other opportunists is mandated by abnormal findings on a chest roentgenogram, most often consisting of a diffuse, hazy interstitial infiltrate.[38] Occasionally the radiographic findings can be quite subtle and rarely is a completely normal chest x-ray study seen in the presence of biopsy-confirmed *P carinii* pneumonia. Additional noninvasive tests that may strengthen the need for further evaluation include restrictive pulmonary functions and a reduction in the diffusing capacity for carbon monoxide as well as diffuse and often extreme pulmonary uptake of gallium (Fred M. Gordon, MD, UCSF, oral communication, May 1983).

The diagnosis is most often established by culture or tissue examination. Identification of one opportunist does not obviate the need to search for other potentially treatable concurrent illnesses. This refers not only to the patients with pneumonitis, but also to patients with colitis who may harbor concurrent nonopportunistic but pathogenic organisms such as *Shigella* or *Campylobacter* but who also have herpes, cytomegalovirus or coccidia colitis (Table 4). As has been stated, these patients not only show profound depression of their T-lymphocyte numbers and function, but also manifest inappropriate immunoglobulin production by the B-lymphocyte population, making serologic diagnosis unreliable. For example, in patients who have aggressive cytomegalovirus infection a falling IgG titer by complement fixation or microimmunofluorescence has been noted as the illness progresses.

Culture methods are readily available for many of these opportunists, including cytomegalovirus, herpes simplex virus, adenovirus, *Legionella, Mycobacterium* sps, *Nocardia, Cryptococcus neoformans, Candida* sps and *Chlamydia.* Many of these organisms have been cultured from a variety of unusual or unexpected sites. For example, *M avium-intracellulare* has been cultured from cerebrospinal fluid, bone marrow, pericardium and blood and from lung biopsy and sputum specimens. The ability to culture this organism from some of these other sites may provide an objective but less invasive way to assess response to therapy. Attempts to culture *P carinii* are undergoing evaluation currently, but no culture method is clinically available.

Tissue diagnosis for some of these infections is mandatory. These include *P carinii* pneumonia and *T gondii* encephalitis. Positive acid-fast stains suggest mycobacterial disease from bronchial specimens, bone marrow

aspirates, lymph node biopsy specimens and various body fluids and excretions, before the diagnosis is confirmed by culture. Newer diagnostic techniques include monoclonal immunofluorescence staining of biopsy specimens and rapid DNA hybridization techniques for cytomegalovirus[39] and herpes simplex virus. To date these remain less sensitive but more rapid than traditional culture techniques.

Space does not permit elaboration of the treatment for these diverse infections. The general approach is outlined (Table 5). Nutrition is a problem despite the fact that many of these patients have an intense desire to fight their illness through dietary management. Although it remains unproved, early attention to nutritional support may be helpful in managing the spectrum of illnesses.

Demanding special comment is the therapy for *P carinii* pneumonia. In previously well-defined high-risk populations this infection has been noted to be equally responsive to either high-dose trimethoprim-sulfamethoxazole or pentamidine.[40] The clinical success rate has been 70% to 90%, depending somewhat on the patient group studied. Of the first 35 patients with AIDS treated at the UCSF hospitals for *Pneumocystis,* less than 15% were able to complete therapy with trimethoprim-sulfamethoxazole to clinical and biopsy-confirmed cure.[41] Serious toxic reaction to trimethoprim-sulfamethoxazole developed in more than two thirds and led to a change of therapy in more than half. The toxic reactions include several with diffuse skin rashes, anaphylaxis, hepatic dysfunction and leukopenia. Trimethoprim or sulfamethoxazole concentrations can be measured. These should be monitored to document adequate absorption of oral therapy or to minimize the toxicity of intravenously given therapy. It has been the experience at UCSF that few patients respond to the standard 14-day course of therapy and an attempt is made to treat for a minimum of three weeks with confirmation of cure by transbronchial biopsy before discontinuing therapy. Some patients have required more than six weeks of therapy to achieve histologically proved cure.

Likewise, antimicrobial therapy for most of the other infectious complications of AIDS can be difficult and prolonged. Disseminated *M avium-intracellulare* often requires four to six drugs that many tolerate poorly and the mortality from this disease, both from the San Francisco experience and across the country, has been high. Cytomegalovirus disease in AIDS has been poorly responsive to antiviral therapy, including acyclovir, which is not unexpected given the lack of in vitro sensitivity to this drug. Despite occasional reports of cases of *Cryptosporidium* responding to high-dose trimethoprim-sulfamethoxazole, no therapy has been proved successful despite trials with several antibiotics, both in animals and in humans.[35] Furazolidone at 100 mg given orally four times a day for seven days has met with some encouraging, but not always achieved, remission of symptoms.

The need for new chemotherapy in many of these infections is recognized. A number of drugs are available on protocol. For treatment of *M avium-intracellulare* these include ansamycin, a congener of rifampin, and clofazimine, which has shown some efficacy in the treatment of leprosy. Immunomodulating therapy such as various interferons, thymosin, transfer factor, interleukins and plasmapheresis are also undergoing preliminary clinical trials in some centers. To date the results of these trials are too preliminary to allow comment in the treatment of opportunistic infections.

TABLE 5.—*Principles of Therapy for Opportunistic Infections in Acquired Immune Deficiency Syndrome (AIDS)*

Early diagnosis by culture or tissue examination
Chemotherapy often more prolonged than "standard"
Several drugs may be required to achieve a cure and *new* therapies are necessary
Toxicity of chemotherapy may be more profound than expected
Confirm cure with reexamination by culture or tissue specimen examination before discontinuing therapy
Nutritional support
? Prophylaxis

In summary, the infectious complications of AIDS are profound and life-threatening. Their appearance in a person suggests a more profound immunodeficiency state than is seen in patients with only Kaposi's sarcoma and carries with it a worse prognosis. Therapy for many of these organisms is in a developmental state as few drugs are available for some of these opportunistic pathogens and many of these are associated with pronounced host toxic reaction. The approach of most clinicians is to attempt early diagnosis, which often requires tissue biopsy confirmation, in the hope of instituting available treatment early and documenting cure microbiologically before discontinuing therapy. It is hoped that in the course of treating these intercurrent problems the underlying immunodeficiency state will resolve spontaneously or that immunomodulating therapy or more specific treatment for the cause of AIDS will appear.

The Use of Blood and Blood Products and Implications for Blood Banking

DR PERKINS:* The possibility that AIDS might be transmitted by blood transfusion was considered very early because of its occurrence in persons with a high incidence of hepatitis and because of apparent spread through multiple use of needles to self-inject drugs. The possibility became still more likely with the recognition of AIDS in persons with hemophilia who were not in any previously recognized high-risk group. The final piece of evidence came from a child here at UCSF whose illness was diagnosed as AIDS. The child had received blood components from 19 donors, one of whom we found listed as a subsequent AIDS victim by the San Francisco Health Department.[5]

We all accept the likelihood that AIDS can be trans-

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mitted by blood transfusion—even though the evidence is circumstantial—but what is the risk? Thus far, 16 hemophiliac patients of the 10,000 to 20,000 in this country have AIDS. All have in common the use of commercial clotting factor concentrates prepared from thousands of units of pooled donor plasma, 80% of which is from the paid donors of plasmapheresis centers. The hemophiliac patients who have AIDS do not have a single lot of clotting factor concentrate in common, and it appears that if the concentrates are responsible for transmitting AIDS, then all lots of all manufacturers are implicated. Each lot is given ultimately to about 100 different hemophiliac persons. Clearly AIDS did not develop in most recipients of those lots and if an infectious agent is involved, most recipients may not be susceptible.

On the other hand many hemophilia sufferers have abnormalities in immunologic tests that resemble those found in patients with AIDS, and the severity of these abnormalities appears to correlate with the quantity of concentrate received in the past. Some evidence suggests that these abnormalities occur primarily in recipients of commercial concentrates and little or not at all after single donor cryoprecipitate.[41,42] Contrarily, in the state of Washington where only cryoprecipitate is used, the same abnormalities are found, and in Scotland where the concentrates come from local donors the same abnormalities are seen even though AIDS has not been recognized in that country. It appears possible that these abnormal test results are the effects of large amounts of intravenously administered concentrate and not a manifestation of AIDS.

The situation is quite different when we turn to the effects of single blood components from volunteer donors. Since our report in December 1982,[5] there have been no further cases in which AIDS developed in both a donor and recipient. There are under investigation in this country 12 to 16 more cases in which patients with a history of blood transfusion have AIDS with no other obvious explanation. Some of the blood received by these patients did come from high-risk group donors, but none of those donors has AIDS and there are no controls to tell us whether the number of high-risk donors was higher than should have been expected at that time. Even if all of these cases are accepted as transfusion-induced, the number of patients receiving transfusions during the same period was 10 to 12 million. Thus the risk of contracting AIDS from a transfusion was in the range of 1 in 1 million before the blood banks began deferring high-risk donors. Clearly the risk of AIDS does not add significantly to the other known risks of blood transfusion.

If AIDS is caused by an infectious agent transmitted by blood transfusion, most recipients may not be susceptible. The donor to the UCSF child with AIDS gave blood twice in the two years before the onset of his disease. Three other recipients have been followed for several years and do not have AIDS. Three other donors have appeared on the city's AIDS list within two years of onset of symptoms. None of their 19 recipients has AIDS. To be sure, several of the recipients mentioned require further observation and testing before we can conclude they are safe. Further observations will continue and we plan to add a control group transfused at the same time using donors in whom AIDS did not develop.

Eliminating persons from high-risk groups as blood donors is a requirement of the Food and Drug Administration and a policy of all blood banks. Irwin Memorial Blood Bank (San Francisco) began to screen out these donors in December of 1982. Much of this was achieved by educating persons in the high-risk groups through their physicians and community news media. Prospective donors now must read an information sheet on AIDS and then answer a questionnaire that allows donors to defer themselves if they have any of the premonitory signs or symptoms of AIDS or have had multiple sexual partners among members of a high-risk group.

There is no test for AIDS, but the CDC suggested in January that blood banks test the feasibility of surrogate tests—those that tend to give abnormal results in most AIDS patients. We have evaluated tests for antibody to hepatitis B core antigen and absolute lymphocyte counts. The New York Blood Center has also checked helper-suppressor ratios, antibody to cytomegalovirus and immune complex levels. Both blood banks have concluded that these tests do not distinguish between the usual acceptable donor and healthy altruistic donors who are members of a high-risk group. Further tests will be explored including serum β_2-microglobulin, thymosins and human T-cell leukemia virus tests.

Some people feel that the ultimate protection is to provide their own donors. Irwin Memorial—along with most blood banks in this country—will not permit this for the following reasons:

1. There is no reason to believe anyone can provide safer donors than the screened altruistic volunteers already supplying blood. In fact, asking a friend or relative to donate blood may force that person to do so, even though—as a closet homosexual—he would otherwise have refrained from donating.

2. There is serious concern that permitting designated donors would lead to large segments of the population withholding donation to be available for a friend or relative. This is more than a hypothesis. Elsewhere in this country a large "blood donation day" at a mobile unit was cancelled on those grounds, though the blood bank had been relying on it for a major portion of its supply for the next few days. The entire blood supply of the country could become inadequate with little notice.

3. Equally serious is the likelihood that a large number of designated donations could so disrupt routine operations as to result in errors that risk patients' lives. The problem is difficult for a community blood bank but worse for a hospital transfusion service whose refrigerator is overloaded with units on reserve for specific patients with tags or special labels that cause confusion and resulting errors.

4. Legally there is no liability in refusing to accept designated donations but accepting designated donations creates legal liability if those components are misdirected.

Nothing I have said argues against the use of specific donors for specific patients when scientifically justified —that is, when compatible components are not otherwise available or when the blood donor will be donating a kidney to the recipient. Preoperative donation for autotransfusion can also be scientifically justified and should be encouraged.

In concluding, I would like to repeat an earlier statement. If AIDS is transmitted by blood, the risk was about one in a million before blood banks refused donations from donors at high risk for AIDS. Currently the risk should be infinitely lower.

Infection Control Implications

Dr Conte: The Ad Hoc Advisory Committee for AIDS and the Infection Control Committee, based at this hospital, and the Infection Control Committee and the University of California Task Force for AIDS at San Francisco General Hospital Medical Center have collectively developed guidelines for the care of patients who have AIDS.

The guidelines are based on a pattern of transmission that closely resembles hepatitis B. Thus, hospital precautions are aimed at minimizing contact with blood and other body fluids and tissue.[43,44]

The definition of AIDS for infection control purposes is as outlined by the Centers for Disease Control:

> Persons with: opportunistic infections that are not associated with underlying immunosuppressive disease or therapy; Kaposi's sarcoma (patients under 60 years of age); chronic generalized lymphadenopathy, unexplained weight loss and/or prolonged unexplained fever in persons who belong to groups with apparently increased risk of AIDS (homosexual males, intravenous drug abusers, Haitian immigrants, hemophiliacs); and possible AIDS (hospitalized for evaluation).[44]

We have included patients with the so-called gay lymph node syndrome because some of these patients have opportunistic infections and others have the full syndrome.

The responsibility for identifying a patient in hospital who may have AIDS rests with attending physicians. Because AIDS is now a reportable disease in California,[45] attending physicians must report this diagnosis to the Public Health Department. Extreme care must be taken in exercising this responsibility because false labeling of patients may lead to serious psychological stress, and failure to identify patients correctly may have serious medical and infection control consequences.

As indicated in the introduction, precautions should be very similar to those appropriate for hepatitis B (Table 6). Casual transmission is extremely unlikely or does not occur. Specimens should have a warning label and should be placed in an impervious bag or container for transportation to a laboratory. At our three teaching hospitals, the Task Force has recommended the label "H/A," which is a code abbreviation for Hepatitis/AIDS. All specimens, however, should be handled with care and regarded as potentially infectious. Gloves should be worn to prevent direct contact with blood, tissue, body fluids or inanimate objects potentially contaminated by them. Frequent handwashing is the mainstay of effective infection control and should be done before and after all contacts. Gowns are recommended for persons likely to have contact with body fluids, excretions or blood. Contaminated inanimate surfaces should be cleaned immediately with a disinfectant such as sodium hypochlorite solution.

TABLE 6.—*Infection Control Measures in Acquired Immune Deficiency Syndrome (AIDS)*

Appropriate Precautions
Handwashing
Gloves
Gowns
Masks for coughing patients
Protective eye wear
Single room for associated infection
Immediate cleaning of blood spills

Masks should be worn by visitors and hospital staff who have direct and sustained contact with an actively coughing or intubated patient. Coughing patients with AIDS should wear a mask when outside their room. This recommendation was made by the Task Force to address the theoretic possibility that *Pneumocystis* or other opportunistic respiratory tract pathogens, perhaps in high inocula in an AIDS patient, might be transmitted to other patients or staff. This position is supported by animal studies that suggest *P carinii* pneumonia may be transmitted by the respiratory route.[46] Personal communications with infection control practitioners in Florida, New York and Los Angeles have indicated varying practices with regard to mask policies.

Protective eye wear is recommended in situations in which blood, bloody secretions or body fluids may be splattered into the eye. This may occur during procedures carried out by physicians, dentists, technicians, nurses and other medical personnel involved in bronchoscopy, endoscopy or oral operations. The precautions for other procedures that may generate aerosols, such as endotracheal intubation, must be judged on an individual basis.

Used needles should not be resheathed and needles and syringes should be placed in a puncture-proof box. Employees with needle-stick injuries should report to an employee health service and be treated according to the needle-stick protocol at their hospital.[47] Because a number of illnesses such as cytomegalovirus-induced mononucleosis, hepatitis B infection and biliary cirrhosis are associated with reversed lymphocytic helper-suppressor ratios,[48-50] the Task Force has recommended that routine follow-up lymphocyte studies should not be done unless for research purposes.

All contaminated disposable items should be considered infectious waste and disposed of according to each hospital's procedures. In this hospital infectious

waste is red-bagged and handled specially by the waste disposal company. Contaminated linen should be double-bagged.

A private room is unnecessary if a patient is not coughing, is cooperative and is in control of bodily functions. It may be prudent to admit patients to private rooms (if available) for reasons other than infection control. Patients with AIDS who are in double rooms should not have an infected or immunosuppressed patient as a roommate.

The diagnosis of AIDS, per se, is not a valid reason for refusing to deliver care to these patients. Health care workers who feel that they may be susceptible to infection should discuss their work responsibilities with their private physician. An employee's department must judge each request for reassignment on an individual basis according to the institution's personnel policies and procedures.

The Task Force was unable to reach consensus regarding direct patient contact by asymptomatic employees who have AIDS. Two alternatives were offered; that is, the hospital could advise reassignment to nonpatient care duties or it could judge each employee on a case-by-case basis. In the latter instance, an employee would be permitted to have direct patient care provided the AIDS employee was completely asymptomatic and was not put at increased risk of acquiring infection while carrying out normal duties.

These guidelines should also be applied to the outpatient and emergency departments. Separate examining rooms or waiting areas are unnecessary; however, efforts should be made to minimize direct contact with other severely immunocompromised patients.

Questions and Answers

Q: *Would Dr Levy comment further on the role of the T-cell leukemia virus?*

Dr Levy:* Two points need to be considered in discussing the possible role of the human T-cell leukemia virus (HTLV) in AIDS. First, it is a type C retrovirus that is found associated with T-cell leukemia. It induces, in culture, a proliferation of human T cells rather than the death of these lymphocytes. Second, the studies that suggested a high incidence of infection by human T-cell leukemia virus in AIDS patients were done using serum specimens from patients with AIDS. The investigators found that when these specimens were mixed with T-cell lines producing HTLV, up to 30% of AIDS patients' serum specimens showed a positive membrane fluorescence.[51] This approach, however, has one very important shortcoming. Because polyclonal B-cell activation occurs in persons with AIDS, the patients produce antibodies against several normal cellular components. Thus, the presumed antibodies to human T-cell leukemia virus could be directed against cellular antigens on the surface of those particular T cells producing the virus; they may not be virus-specific. Many more controls need to be assessed before one can conclude that human T-cell leukemia virus infection is prevalent in AIDS. Nevertheless, there have been similar retroviruses identified from three or four patients with AIDS or lymphadenopathy.[52,53]

Q. *Has any patient regained their normal immune competence after the diagnosis of AIDS was made?*

Dr Ammann: I am not aware of any patient group, either those who have AIDS per se or who have the lymphadenopathy syndrome, where there has been a significant improvement in the immunodeficiency. Keep in mind, however, that follow-up studies of more than one year are just now being completed. Early results show that either there is a worsening of immunologic function or no change.

Q: *Should otherwise healthy gay men undergo some sort of screening test to anticipate the possibility of AIDS?*

Dr Volberding: We have a screening clinic at San Francisco General Hospital Medical Center that serves the purpose of educating people who are concerned about the possibility of contracting AIDS about the appropriate measures that we think can reduce risk. It is probably not very useful in identifying someone at a stage where therapy really makes no difference.

Q: *Are fatal AIDS cases routinely autopsied?*

Dr Volberding: Yes.

Q: *What is the role of adenosine deaminase and purine nucleoside phosphorylase in the acquired immune deficiency syndrome?*

Dr Ammann: We have looked at these enzymes and have found them in normal quantities in cases of acquired immune deficiency syndrome. The possibility that purine nucleoside phosphorylase might be deficient is intriguing because a deficiency of that enzyme is associated with elevated immunoglobulin levels and T-cell deficiency, a pattern that is identical to what is seen in cases of AIDS. One could theorize that certain infectious agents might produce similar alterations in biochemical patterns, but so far this approach has not been helpful in identifying a cause.

Q: *Is AIDS one illness or a group of diseases with similar characteristics?*

Dr Levy: AIDS appears to be an illness caused by an infectious agent that destroys part of the immune system. An important observation is that the vast majority of persons affected by this disease fit primarily into five risk groups: homosexual or bisexual men, intravenous drug abusers, persons with hemophilia, Haitian immigrants and newborn children. AIDS has rarely affected persons outside these subgroups of the population and thus does not have a random distribution. One then has to ask what is common about these risk groups. One answer is that AIDS patients come from subgroups

*Jay A. Levy, MD, Associate Professor of Medicine and Research Associate, Cancer Research Institute, UCSF.

whose healthy members, as discussed earlier, are already immunocompromised by previous exposure to multiple infectious agents, drugs or blood products or, in the case of children, are immunonaive.[54] Thus, the agent responsible for AIDS appears to be primarily pathogenic in someone whose immune system is already compromised. AIDS, itself, therefore, is an opportunistic infection.[54] Why is this point important? Because it emphasizes that the risk of a healthy person getting AIDS is incredibly low. It would also predict that many of us have already been exposed to the agent and are carrying antibodies to it, since we have successfully resisted the disease.

Why patients with lymphadenopathy are primarily gay men could be explained by the fact that gay men often have a myriad of infections—hepatitis, herpes—that induce this symptom and also contribute to an immunocompromised state. Lymphadenopathy could result from an attempt of a host to ward off AIDS infection, but I believe it primarily reflects infection by other agents. Affected persons should recognize, however, that they are at risk of getting AIDS. With this condition, if exposed to the AIDS agent, their immune system would have difficulty in resisting the infection. Thus, patients with lymphadenopathy are advised to adopt a life-style that would prevent them from encountering the AIDS agent and would enable their immune system to recover.

Why Kaposi's sarcoma is found primarily in gay men is an intriguing question. Because cytomegalovirus antibodies and infectious virus can be found in probably all homosexual men with AIDS and the virus has been detected in Kaposi's sarcoma tissues, we suggest that the emergence of malignant Kaposi's sarcoma is linked to an activation of cytomegalovirus.[54]

Dr Ammann: I would like to emphasize what Dr Levy said. I think we miss a very important point in the hemophilia story. Dr Perkins emphasized that there are few hemophiliac patients in whom AIDS, as defined by the CDC, has developed when compared with the number of infusions they get. This is telling us that AIDS may be a double-hit mechanism: There may be a single AIDS agent that induces an underlying immunodeficiency. This is followed by multiple hits with other infectious agents that eventually result in AIDS. The hemophilia population has the first hit, as a result of multiple transfusions. Most of them therefore have abnormal immunologic findings, but they do not go on to have AIDS. This is because they do not have the infectious disease exposure that is characteristic of AIDS patients.

Dr Volberding: There are almost certainly genetic contributions to explain why men so much more often than women get this disease; this is true of traditional Kaposi's as well, which affects men more often than women in a ratio of 20:1.

Q: *Are exogenously immunosuppressed populations at risk for Kaposi's sarcoma or AIDS developing?*

Dr Volberding: We have not seen Kaposi's sarcoma in our own transplant population. It is really the Toronto experience that suggests that Kaposi's sarcoma is transplantation related, plus cases from Israel. I do not know if anyone has looked at differences in the demographics of the transplant population in Toronto and in other places. I would not be surprised to learn that there is a higher incidence in Jewish patients there. If true, this might again suggest a genetic relationship because traditional forms of Kaposi's are seen in people of Mediterranean-Jewish descent.

Dr Levy: I would like to present an alternative view to the absence of immunosurveillance as a cause of Kaposi's sarcoma. The disease could result from immune stimulation.[54] We need to ask why we are observing primarily lymphomas and Kaposi's sarcoma, and not other cancers, in AIDS patients. Kaposi's sarcoma appears to be an endothelial cell tumor, and endothelial cells have several characteristics in common with immune cells. Thus, they may be part of the immune system. Possibly, Kaposi's sarcoma results from an attempt by an AIDS patient's body to bring the immune system back into balance. Higher levels of interferon and thymosin are found in the blood of AIDS patients.[54] Conceivably, other immunomodulating factors are produced in increased amounts and they, like the prostaglandins for instance, could have angiogenesis activity. Thus, these regulating substances, produced in response to the immune deficiency in AIDS, could induce a proliferation of endothelial cells. This event could then lead, perhaps coupled with activation of cytomegalovirus, to the development of malignant Kaposi's sarcoma.

This alternative hypothesis would also predict that if you bring the immune system back into balance, the production of these angiogenesis-promoting factors would be decreased and the tumor, which is probably hormone dependent, would disappear.[54] The lymphomas occurring during immune suppression could also result from the production of certain stimulating substances by the immune system in an attempt to bring itself back into balance. In these forms of cancer, the role of Epstein-Barr virus in the malignant transformation of B cells needs to be considered.

Dr Perkins: I would like to comment further on Dr Ammann's multiple-hit hypothesis, which I think we all have to accept one way or another. Dr Ammann postulated that hemophiliac persons are first infected by AIDS and then are susceptible to a wide variety of infectious agents to which they are subsequently exposed. However, hemophiliac patients are being exposed repeatedly to many other viruses, and I would expect to see more persons with hemophilia in trouble if AIDS were the first hit. I hypothesized the opposite: that hemophiliac persons first have either viral infections or nonspecific effects of the clotting factor concentrates. These affect their immune responsiveness and leave

them susceptible so that some of them eventually do get AIDS.

Q. *Can you comment further on the role of genetic factors and the risk of acquiring AIDS?*

Dr Volberding: Of the four sets of identical twins that we have studied, in all cases one has AIDS and one does not. Two of the sets are both gay whereas in the other sets only one of the twins is gay. Genetically they are, of course, identical, and from studies that Art Weiss has done in John Stobo's laboratory, they do not react to each other's cells.

Q: *Is human leukocyte antigen subtyping being done?*

Dr Volberding: We did that initially, but we are not doing it on a continuous basis. There has been a great deal of controversy in New York about human leukocyte antigenic subtypes predisposing to AIDS itself or to different manifestations of AIDS. I think that the data are still too preliminary to comment on.

Q: *Are there proteins in sperm and factor VIII that might actually be immunosuppressive?*

Dr Levy: There are two observations that are important to consider. One is the interesting finding that several patients dying of AIDS have atrophy of the testes. Second, it has been reported that when mice are inoculated with sperm, they make antibodies to T cells.[55] There appears to be a shared antigen between sperm and T cells. The problem with this idea is that we cannot explain all the cases of AIDS on that basis. What we can say is that sperm, particularly introduced via the anal canal, could be one of the contributing factors that leads to a baseline immunocompromised person who then would be susceptible to the AIDS agent.[54]

Dr Perkins: The factor responsible for AIDS is probably not the factor VIII protein itself. Although AIDS has not been reported in hemophilia B (Christmas disease) patients who are treated with factors II, VII, IX, X concentrate, I have been told that there is one such case in Long Island that has not yet been reported. The effect of the factor VIII concentrates could be nonspecific. γ-Globulin is given intravenously to treat idiopathic thrombocytopenic purpura on the grounds that it provides nonspecific reticuloendothelial blockade. I suspect that almost anything administered intravenously (certainly most blood products) results in some temporary immunosuppression.

Q: *Would you comment on the use of hepatitis B vaccine vis-à-vis AIDS, and on the incidence of AIDS in health care workers?*

Dr Perkins: The Centers for Disease Control have stated that hepatitis B vaccine is safe even though the plasma used to make current batches is largely from gay donors. The empty protein coats are purified and then subjected to three separate viricidal procedures. It is difficult to believe that an infectious agent could survive these processes. The early vaccine trials provided no evidence that the vaccine transmitted AIDS. Those trials were in gay groups and, in fact, more AIDS occurred in the control group than in the group that had received the vaccine. A related product, hepatitis B immune globulin, comes from the same donor source, and is not subjected to any sterilizing procedures; however, there have been no known cases of AIDS attributed to it.

Q: *Dr Dritz, would you like to comment on the cases of AIDS in health care workers?*

Dr Dritz: The CDC recently reported four cases of AIDS in health workers who had no apparent prior reason for being immunosuppressed. CDC also announced, however, that they could not be sure that all of the histories were entirely accurate; there were possibilities of needle sticks and of other exposures, though nothing was definitely proved. Here in the Bay Area I have nine health workers in my roster, but all of them had other usual risk factors for AIDS.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Nissen's Fundoplication With Gastric Reservoir Reduction

QUESTION:

Is the surgical procedure known as Nissen's fundoplication with gastric reservoir reduction by means of gastric Teflon wrap accepted medical practice for the treatment of morbid obesity?

OPINION:

In the unanimous opinion of the Scientific Advisory Panels on General Surgery and Internal Medicine, Nissen's Fundoplication with gastric reservoir reduction by means of gastric Teflon wrap is not considered established medical practice for the treatment of morbid obesity. This relatively new, little-used technique is one variation of a large series of different operations on the stomach to control obesity. The reported complication rate associated with this technique is excessively high, reversibility is difficult and the long-term effects on weight loss are unknown.

This procedure should be considered investigational and performed only as part of a strictly controlled research protocol.

Epitomes

Important Advances in Clinical Medicine

Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in chest diseases that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 44 Gough Street, San Francisco, CA 94103

Strange Causes of Asthma

THE REVERSIBLE AIRWAYS obstruction of asthma can be induced by a large number of well-known provocative factors. These include exposure to familiar inhalant allergens, chemical or physical irritants, cold air, exercise, viral respiratory tract infection, emotional factors and, less commonly, dietary ingestion of food allergens. In some patients, intermittent soiling of the tracheobronchial tree by aspirated gastroesophageal contents can be an important cause of exacerbation of asthma. Not infrequently, attacks of asthma occur "out of the blue," with no apparent precipitant. Chronic cough can be a major (or the only) symptom of asthma, which, though not necessarily associated with reversible bronchospasm, can be documented by evidence of airways hyperreactivity when a patient is tested with certain inhalants ("cough-variant asthma"). Rarely, asthma may be mimicked by paroxysmal glottic obstruction that can be self-induced ("factitious asthma") or functional. Occasionally, true asthma may be provoked by strange or unusual causes that could escape the notice of patients and physicians unfamiliar with their asthmogenic potential. Some of these unusual or unsuspected causes of asthma include food additives, alcoholic beverages, certain drugs, iodinated radiographic contrast material, hemodialysis (due to acetate dialysate or complement-activation by cuprophane), domestic exposure to urea-formaldehyde foam insulation and a variety of occupational exposures (see below).

Food additives implicated in asthma include tartrazine dye, monosodium glutamate ("Chinese-restaurant asthma") and bisulfite preservatives, particularly when used in relatively high concentration as in restaurant foods, dried apricots or the processing of beer and wine; sulfur dioxide (SO_2) generated by the reaction of these sulfites with water provokes bronchospasm in some patients. Alcoholic beverages can induce bronchospasm due to adulterants in the beverage or, rarely, the ethanol itself. Commonly used drugs that can provoke asthma include aspirin and nonsteroidal anti-inflammatory agents; β-adrenergic antagonists (including timolol eye drops); drugs containing tartrazine (FD&C yellow No. 5) colorant additive; aqueous solutions of isoproterenol, isoetharine and metaproterenol containing metabisulfite preservative (from which liberated SO_2 could lead to "paradoxical bronchospasm"), and pancuronium bromide. Patients with asthma who have aspirin intolerance should be provided a list (available on request from the author, D. P. Tashkin, MD, Dept of Medicine, Center for the Health Sciences, UCLA School of Medicine, Los Angeles, CA 90024) of the more than 200 prescription and proprietary compounds that contain aspirin, most of which are combination products.

The prevalence of occupational asthma has risen dramatically in recent years due to the expanding list of asthmogenic substances used or generated in industry. In addition to gaseous irritants, animal proteins, grains, flour, gum, woods, drugs and enzymes, these substances include a number of low-molecular-weight compounds that may act as haptenes to produce immunologically mediated asthma: reactive dyes (including methyl blue in electrocardiographic ink); ethylenediamine (shellac, photographic chemicals); phthalic anhydride (paint, epoxy resins, meat wrapping); abietic acid (solder flux fumes leading to "colophony-induced asthma" in electronics workers); toluene diisocyanate (polyurethane foam, varnish), and other isocyanates

(automobile spray paint, laminates). Physicians need to be alert to the possibility that "strange" causes of asthma may lurk in increasingly complex workplaces.

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Bronchoscopy and Lasers

Fluorescence bronchoscopy is a sensitive method to locate small mucosal or intrabronchial cancer lesions not found on routine bronchoscopy in patients with positive sputum cytology studies and normal findings on chest x-ray films. Diagnosis is warranted at this early stage (stage 0, or $T_{IS}N_0M_0$) because resection may be expected to be 90% to 100% curative. With this method hematoporphyrin derivative, which is retained within cancer cells (of all histologic types, primary or metastatic), is injected intravenously. The fluorescence bronchoscope uses violet light (410 nm) from a krypton ion laser, conducted via a fine quartz fiber (0.4 nm) in its suction channel, to its tip. Fluorescing lesions are visualized with an image intensifier, are then brushed and a forceps biopsy done for specific diagnosis.

Photoradiation therapy for endobronchial tumors by bronchoscopy uses the photodynamic action of hematoporphyrin derivative within tumor cells to produce singlet oxygen when activated by red light (630 nm) conducted via a quartz fiber from an argon-pumped dye laser. Power is low (200 mW), and there is no immediate visible change or coagulating effect. Cell and cell membrane function are gradually impaired so that tumor cells die over the next 24 to 48 hours. Tumor debris is then removed by repeat-bronchoscopy, to open up the bronchus to its full extent. Even a totally occluded bronchus can be fully opened up, and an atelectatic lung, lobe or segment may be re-aerated. Methods of light application developed are effective and efficient; generally (80% to 90% of cases) only one treatment is required. There have been no complications during photoradiation treatment of obstructing endobronchial tumors. Photoradiation therapy for early bronchial cancer is potentially curative, and clinical trials are under way.

Photocoagulation therapy uses pulses of a beam of intense (20 to 40 W) infrared light (1,060 nm) from an Nd-YAG laser. Tumor tissue is thereby immediately coagulated by heating (50°C to 60°C), or can be vaporized (100°C) by higher power (40 to 90 W). Large obstructing tracheal and main bronchus tumors after coagulation can be sheared off by the tip of the rigid bronchoscope. Tumors and granulation tissue masses and fibrotic stenotic areas caused by an endotracheal tube or tracheostomy can be vaporized. The tip of the fiber must be carefully aimed to prevent penetration of the wall, hemorrhage and possible death.

These new advances in bronchoscopic laser therapy are effective and safe in experienced hands. Still to be documented are patient benefits in terms of survival, the duration of control of the tracheobronchial lesions and whether they recur, the degree of improved breathing and lessened cough and the prevention of recurrent respiratory tract infections and distal pneumonia.

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Drug Therapy for Pulmonary Hypertension

THE TREATMENT of pulmonary hypertension depends on its cause and includes such diverse measures as anticoagulant or fibrinolytic therapy for pulmonary embolic disease; oxygen, bronchodilators and pulmonary hygiene for patients with chronic obstructive pulmonary disease, and surgical treatment for patients with congenital heart disease and mitral stenosis. There is some evidence that the use of the bronchodilator terbutaline sulfate may decrease pulmonary vascular resistance and lessen the load of the right ventricle in patients with chronic obstructive pulmonary disease.

A variety of vasodilator drugs have been used with varying success in the treatment of primary pulmonary hypertension and other forms of pulmonary hypertension. These include tolazoline hydrochloride (25 mg every four to six hours), isoproterenol hydrochloride (10 to 20 mg sublingually every three to four hours), hydralazine hydrochloride (25 to 75 mg every six hours), diazoxide (100 to 200 mg every 8 to 12 hours) and, most recently, nifedipine (10 to 40 mg every six hours). Individual patient response is influenced by the summation of pharmacologic effects on the systemic and pulmonary circulations. These vary from person to person. Vasodilators may reduce pulmonary vascular resistance and pulmonary artery pressure may not change if the cardiac output increases as the pulmonary vascular resistance falls.

Alternatively, pulmonary artery pressure may increase in patients in whom systemic effects predominate, resulting in a fall in systemic vascular resistance and increased cardiac output without a simultaneous fall in pulmonary vascular resistance. Initiation of therapy for primary pulmonary hypertension requires heart catheterization and the careful hemodynamic assessment of individual patient response to specific drugs.

Total heart-lung transplantation has been successfully completed in victims of primary pulmonary hypertension and is an experimental form of treatment that holds promise.

To develop a better understanding of the natural history, pathophysiology and response to therapy of

primary pulmonary hypertension, a national registry of cases and a cooperative, multicenter study group has been established. Information regarding referral of patients into the study may be obtained by writing to Primary Pulmonary Hypertension Registry, c/o Chief, Interstitial Lung Disease Branch, Division of Lung Diseases, National Heart, Lung and Blood Institute, Westwood Bldg, 6A03, 5333 Westbard Avenue, Bethesda, MD 20205.

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Staging of Lung Cancer

In view of variations in published survivorship data for patients with lung cancer with regional nodal involvement—that is, hilar-mediastinal—advances in prethoracotomy diagnostic techniques and the lack of uniformly accepted anatomic definitions of each regional-pulmonary nodal station, the American Thoracic Society formed a committee on lung cancer and charged it to:

- Develop a map of regional pulmonary lymph nodes that would be acceptable to all physicians who care for patients with lung cancer.
- Develop multifactorial criteria for the extent, degree and type of nodal involvement in cases of primary lung cancer.

The recommendations of this committee, with respect to these two charges, were recently published. A map of regional pulmonary nodes was presented and the anatomic definitions of each nodal station were tabulated. It was recommended that this mapping technique be adopted to ensure uniformity in recording and publishing patient data. Only then can surgical series be compared and the impact on five-year survival determined. Such prospective data may allow clearer definition in the future of the criteria for surgical resection.

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Nonsurgical Treatments for Sleep Apnea Syndromes

Sleep apnea syndromes involve a complex of manifestations that often interact progressively, threatening a patient's comfort, functioning and occasionally life. Such features include sleep fragmentation, autonomic nervous system stimulation, cardiovascular changes and pulmonary dysfunction. A thorough medical evaluation, including imaging of the upper airway, is necessary to determine the efficacy of treatment, the evaluation being directed at part or all of such perturbations, carefully defining the importance of local anatomic abnormalities and of central or effector system impairment.

Approaches to managing sleep apnea syndromes have included surgical and mechanical corrections (not considered in this article), oxygen therapy, weight reduction where appropriate and the use of a variety of medications. Evaluation has been applied to at least the following medicines:

- Clomipramine hydrochloride,
- Protriptyline hydrochloride,
- Medroxyprogesterone acetate,
- Acetazolamide,
- L-Tryptophan,
- Theophylline ethylenediamine (aminophylline),
- Naloxone hydrochloride,
- Bromocriptine mesylate,
- Strychnine,
- Almitrine.

Conclusions concerning efficacy may be broadly divided into those with predominantly central (or diaphragmatic) or predominantly obstructive causes.

1. No one has reported that drugs alone have completely resolved a severe obstructive or central syndrome in which apnea is continuous and associated with significant repetitive oxygen desaturation during sleep.

2. Weight loss alone in obese persons has led to the disappearance of a predominantly central or a predominantly obstructive sleep apnea syndrome in specific, selected cases. Low-flow oxygen given during sleep in conjunction with weight loss, again in selected cases, particularly in predominantly central or mixed syndromes, has helped to halt significant oxygen desaturation during the weight loss period.

3. Some drugs have essentially no effect, such as bromocriptine (given for obstructive apnea), naloxone (for obstructive apnea; reports conflict regarding predominantly central problems but even in these cases most results are negative) and almitrine (for obstructive apnea).

4. Other drugs have been beneficial *in certain cases.* Aminophylline has been helpful in treating central apnea associated with cardiac failure. (In only one article is central apnea clearly distinguished from the Cheyne-Stokes breathing pattern, which is also alleviated by aminophylline). Strychnine has been reported effective in non-rapid-eye-movement (NREM) sleep apnea, but it has only been tried in three patients. Acetazolamide is helpful in treating central sleep apnea at high altitudes, but its efficacy in cases of central apnea at sea level is questioned. L-Tryptophan, which also affects sleep, has been helpful when taken in 3- to 5-gram doses before bedtime in mild or moderate central and mixed apnea syndrome, particularly in the elderly. The tricyclic medications (initially clomipramine, more recently protriptyline) have been reported effective in mild to moderate central, mixed and obstructive syndromes since 1970. Presently protriptyline, 10 to 20 mg, is most commonly prescribed to be taken at bedtime. It affects muscle tone and rapid-eye-movement (REM) sleep, but the well-known tricyclic antidepressant side effects, particularly

in the elderly, and the need to take the drug for a long period have limited its prescription. Similarly, medroxyprogesterone given in selected cases of predominantly central or mixed sleep apnea syndrome has proved efficacious, probably because of its effect on central respiratory drive and its diuretic effect. It also helps obese patients who have a combination of obesity-hypoventilation syndrome during sleep and heavy snoring with obstructive hypopnea. The prescribed daily dosage varies between 60 and 150 mg.

In conclusion, medical treatment may be effective for mild to moderately severe sleep apnea syndromes, particularly if imaging does not indicate a significant narrowing of the oropharyngeal airway during the awake state and if a patient is not excessively obese. A combination of treatments can be considered after a complete investigation. The most common are weight loss with or without low-flow oxygen and medroxygesterone, weight loss with or without low-flow oxygen and protriptyline (less frequently prescribed because of the eventual increase in appetite with protriptyline) and L-tryptophan and low-flow oxygen.

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Adverse Drug Interactions With Theophylline

SEVERAL DRUGS can increase the activity of the hepatic cytochrome P-450 system, resulting in a more rapid elimination of theophylline. The serum level of theophylline may thereby be decreased, and inadequate control of bronchospasm can be expected. The dosage requirements of theophylline may be almost doubled with heavy smoking of marijuana or cigarettes and a return to normal may gradually occur over many weeks after smoking cessation. Other drugs that clearly increase theophylline elimination are phenytoin, which may reduce the serum theophylline level by 75% if given for ten days, and phenobarbital, which has less effect. A diet high in charbroiled protein or where there is a significant reduction in coffee intake can cause an increase in the rate of theophylline excretion. In contrast, theophylline use may cause a reduction in the serum concentration of phenytoin or lithium when given with either of these drugs, and their dosages may need to be increased.

Drugs that impair hepatic excretion of theophylline include cimetidine, troleandomycin, erythromycin, allopurinol (when given in a dose of 600 mg a day for at least two weeks) and possibly propranolol hydrochloride. Only cimetidine and troleandomycin are of major concern as theophylline serum concentrations can be doubled by using these drugs, thereby resulting in the possibility of severe theophylline toxicity. Erythromycin can cause less of an effect, but clinical vigilance should be heightened when giving this antibiotic concurrently.

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Current Treatment of Pulmonary Tuberculosis

IN THE TREATMENT of pulmonary tuberculosis, isoniazid in combination with ethambutol is successful in 95% of patients who complete 18 to 24 months of chemotherapy. Although these statistics are excellent, actual results achieved have fallen short of this ideal. The major reason for treatment failure is related to neither the organisms nor the drugs but rather to lack of patient compliance. It has been shown that about 25% of patients do not complete 18 months of therapy. This frequency of premature termination of treatment, among other reasons, stimulated research into shorter courses of chemotherapy. Before the advent of rifampin, however, all attempts to shorten the duration of chemotherapy for tuberculosis resulted in unacceptably high relapse rates.

The bacteriologic basis of chemotherapy for tuberculosis is best understood by considering two populations of organisms: a rapidly dividing group of extracellular organisms and a more slowly growing pool in solid caseous material and within macrophages. Chemotherapy must be prolonged to effectively sterilize this latter pool of "persisting" organisms. Rifampin seems to be uniquely effective against this population of slow or intermittently active organisms, as shown in simulated conditions of intermittent growth in vitro. Field trials in many parts of the world have demonstrated the efficacy of 9- to 12-month regimens containing isoniazid and rifampin, with reported relapse rates of less than 5%.

Isoniazid (10 mg per kg of body weight to a maximum dose of 300 mg a day) taken orally, plus rifampin (10 mg per kg to a maximum dose of 600 mg a day) taken by mouth daily for 9 to 12 months, and for a minimum of 6 months after proved bacteriologic sputum conversion, are now recommended for initial treatment of persons with uncomplicated pulmonary tuberculosis due to drug-susceptible organisms. For persons in whom there is suspicion that the disease is caused by isoniazid-resistant organisms (such as those who have immigrated from an area of high prevalence of primary isoniazid resistance), it is necessary to begin therapy with three drugs, adding ethambutol (15 mg per kg), until results of drug susceptibility tests are available. Except for patients with renal insufficiency, ethambutol adds little to the toxicity of the regimen and offers a safeguard against the possible development of resistance to both isoniazid and rifampin. If susceptibility to all drugs is shown, ethambutol may then be discontinued. At present, short-course chemotherapy cannot be recommended for tuberculosis caused by drug-resistant organisms. If supervision can be insured, then the isoniazid-rifampin regimen may be modified

without loss of efficacy by administering the drugs daily for one to two months, then twice a week for seven to eight months. When given twice a week, the isoniazid dosage should be 15 mg per kg and rifampin, 10 mg per kg, to maximum doses of 600 mg.

With the use of isoniazid and rifampin, 90% to 95% of patients can be expected to have negative sputum cultures after three months of therapy. Bacteriologic evaluation should be done at this three-month juncture to determine if conversion has occurred. Persistently positive sputum cultures may suggest poor compliance or drug resistance. In some patients who have extensive disease, sputum conversion may take longer. Therapy may be stopped six months after sputum conversion, though it may be wise to continue for longer periods if there is continuing radiographic resolution.

Although there is no definite evidence for an increased risk of hepatotoxic effects with this regimen, some authorities recommend that it not be used in persons with acute hepatitis or severe underlying liver disease. Alcohol ingestion should be discouraged but is not a contraindication to using isoniazid and rifampin.

To date, there is little information on the use of rifampin in children, but preliminary data suggest that the nine-month isoniazid and rifampin regimen is equally efficacious and nontoxic if the previously described doses are used. Toxic effects on the liver appear to be more common with rifampin doses of 15 mg per kg of body weight or more.

Finally, although relapse rates have been remarkably low (1% to 4%), short-course therapy is still new and long-term follow-up data are not available. Until more information becomes available, patients should continue to be evaluated for 12 months after discontinuance of therapy. A review of symptoms, a chest roentgenogram and bacteriologic examination of sputum at 6 and 12 months should suffice to document a successful outcome.

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Invasive Diagnostic Approaches to Pulmonary Infiltrates

PATIENTS CAN PRESENT with focal or diffuse pulmonary infiltrates as a manifestation of either specific pulmonary or general systemic disease. Infiltrates can appear patchy, nodular or dense. The most common causes of pulmonary infiltrates are acute infection, tumor and the many disorders that cause chronic diffuse infiltrative lung disease. In essence, findings on a chest roentgenogram are almost always nonspecific and the initial diagnosis depends on the clinical setting, results of laboratory tests (cultures and cytologic and serologic tests) or the response to empiric therapy. The great majority of patients with pulmonary infiltrates have straightforward infectious pneumonia or their disorder is diagnosed by other (noninvasive) tests.

Patients in whom an invasive diagnostic approach may be necessary include those with possible infectious disease who are unresponsive to empiric therapy after a reasonable period of time (days to weeks); immunocompromised patients (including those with the acquired immune deficiency syndrome [AIDS]) with suspected pulmonary infection of unknown cause; those in whom there is a high probability of neoplasm, and patients who have chronic diffuse infiltrative lung disease. Invasive diagnostic pulmonary procedures are appropriate only when there is the expectation that the findings may significantly alter treatment plans.

Three primary ways to obtain a pulmonary tissue specimen are percutaneous needle aspiration biopsy, fiberoptic bronchoscopy and open-lung biopsy. Trephine and needle core biopsy are less useful because of increased complication rates.

The choice of technique depends on four factors, the first being the type of specimen desired and the quality and location of the infiltrate. A percutaneous needle aspiration biopsy produces a cytologic specimen with insufficient tissue to show histopathologic architecture. (Newer aspirating needles may produce useable tissue.) It is an excellent technique for diagnosing infection or neoplasm in peripheral nodules. For diffuse infiltrates wherein infection is suspected the procedure can be done at the bedside without fluoroscopy. Obviously, chronic diffuse infiltrative lung disease cannot be diagnosed by this technique. Fiberoptic bronchoscopy using a Bartlett catheter can provide accurate bacterial diagnosis (aerobic and anaerobic) of lower respiratory tract infections. Bronchoalveolar lavage is remarkably productive in diagnosing infection and is currently the technique of choice in diagnosing *Pneumocystis* pneumonia in patients with AIDS (80% to 90% yield). Transbronchial biopsy can diagnose sarcoidosis in 60% to 85% of patients but is less effective for diagnosing chronic diffuse infiltrative lung disease (35% to 40%). A transbronchial biopsy in an immunocompromised host with pulmonary infiltrates of unknown cause provides a specific diagnosis in only 25% to 30% of patients. Open-lung biopsy is the gold standard: A large piece of tissue can be obtained for culture and histopathologic examination and the surgeon has an opportunity to grossly examine part of the lung. Not all areas are sampled, however, and the results are often nonspecific (5% to 10%), especially in immunocompromised patients with diffuse pulmonary infiltrates (45%).

Second, the choice of technique is greatly affected by the tempo of disease or of patient deterioration. If the process is explosive or a patient is regressing into respiratory failure, open-lung biopsy is often the *initial* procedure of choice. Such situations encourage earlier attempts at diagnosis.

Third, risks must be considered. Percutaneous needle aspiration biopsy has an associated death rate of about 0.1%. In 25% of patients a pneumothorax develops

and 25% to 50% of these require a thoracostomy tube. Fiberoptic bronchoscopy with transbronchial biopsy has an overall death rate of 0.1% to 0.2%. Pneumothorax occurs in 5% to 10% of patients. Brisk bleeding is uncommon. Open-lung biopsy in cases of chronic diffuse infiltrative lung disease has a mortality of 1% to 2%. This procedure requires general anesthesia.

Finally, the choice of the invasive diagnostic approach depends on the skill of the physician doing the procedure. Clearly, a lack of familiarity with the technique increases the risk to a patient and may impede the securing of diagnostic material.

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Management of Childhood Asthma

ASTHMA IN CHILDHOOD originates from a variety of intrinsic and acquired factors that cause bronchial hyperreactivity and impair airways clearance on a chronic, recurrent basis. Respiratory tract disease or injury in early infancy may result in this syndrome, which can persist into adulthood as recurrent bronchospasm or permanent loss of elastic recoil with chronic emphysematous changes.

Although asthma clinically exhibits a continuum of respiratory impairment, newer therapies are directed toward both the acute and chronic states of the syndrome.

Status asthmaticus is a medical emergency. The basic principles of treatment are unchanged and include correction of hypoxemia, adequate hydration and treatment of the underlying infection. While repeated epinephrine injections have been the mainstay of emergency bronchodilator therapy, more recent evidence supports the equal efficacy of inhaled long-acting β_2-adrenergic agents such as albuterol and fenoterol. A greater degree of bronchodilation, longer duration and less adverse reactions represent clear advantages of these agents. Continuous intravenous administration of theophylline ethylenediamine (aminophylline; dosage range, 0.65 to 0.85 mg per kg of body weight an hour, validated by serum concentrations of 10 to 20 μg per ml), corticosteroid infusion and, on occasion, intravenously given isoproterenol have reduced the need for assisted ventilation and the mortality in childhood status asthmaticus.

Much effort has been put into the management of chronic asthma in children. Optimal management reduces impairment, promotes growth and reduces the incidence of life-threatening episodes of respiratory failure. Theophylline given by mouth remains the principal medication indicated in maintenance therapy. Blood theophylline analysis by high performance liquid chromatography (HPLC) allows titration of dosages to suit individual patients. Compliance and continual efficacy are improved with the use of sustained-release tablets and granules that are better absorbed, enhance bronchodilation and increase palatability on a 12-hour (versus 4- to 6-hour) schedule. Inhaled β_2 agents (via portable nebulizer for young children or hand-held metered-dose devices for older children) are helpful supplemental therapies. The long-acting agonists are particularly important in this context, providing sustained bronchodilation with little rebound bronchospasm. Oral β-agonists may be used but are less desirable because of the adverse effects. Short-course corticosteroid administration has been shown to abort impending status asthmaticus with little impact on adrenal function.

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Editorials

Too Many Lawyers?

THE *AMA News* (September 16, 1983) reports that the American Bar Association (ABA) is concerned about the increase in the number of lawyers, having estimated that by the end of 1983 there would be 650,000 lawyers in the United States and by the mid-1990s they will number 1 million. The ABA is worried that this rapid increase in the number of lawyers "may lead to a decline in the image of lawyers and more client complaints if lawyers resort to shortcuts or delay tactics to keep their incomes up, according to *U.S. News and World Report*." There may be others who worry, or ought to be worrying, about the economic impact of such a dramatic increase in the number of lawyers. A more or less comparable percentage increase in the numbers of doctors in more or less the same time frame has caused considerable public discussion about the effect this increase might have on the costs.

A precise breakdown of costs for either the health care system or for the legal system is difficult to come by. At the moment more attention is being given to the costs of health care. Its total costs have been linked to the gross national product and are now said to be more than 10% of it. But it is hard to believe that the total costs of our legal system are not of a similar order of magnitude (even if one chooses to overlook what seem to many to be unconscionable awards in some liability suits), and it is also hard to believe that a rapidly increasing number of lawyers will not have an economic impact upon the total cost of the legal system to the public.

More attention is needed to these issues. The costs of the legal system are surely as important to Americans as is the cost of health care. But the present social and political climate being what it is, it seems unlikely that the legal system and the legal profession will be asked the same kind of questions about costs as are being asked of the health care system and the medical profession. In the meantime there would seem to be many other good reasons to be as worried about there being too many lawyers as is the ABA.

MSMW

The Changing Natural and Surgical History of Abdominal Aortic Aneurysms

THE CAUSE OF ARTERIAL ANEURYSMS, especially aneurysm of the abdominal aorta, is indeed poorly understood, as described elsewhere in this issue by Fortner and Johansen in their comprehensive discussion. Only a relatively small percentage of patients have associated occlusive arteriosclerotic disease of the lower extremities, but the coincidence of abdominal aortic aneurysm with coronary artery disease is high. It is a verifiable fact that more aneurysms have been identified in elderly patients in the past two decades, but whether this represents the accidental discovery because of more abdominal and back x-ray films, more ultrasonic studies and more computed tomographic (CT) scans, or the increased number of persons reaching geriatric age is uncertain.

Surgical results have improved progressively over the past 20 years. This has influenced the decisions concerning prophylactic surgical procedures. Sixty-year-old patients with small 4- to 5-cm aneurysms some years ago were followed till the aneurysms reached 6 to 8 cm, then operation often became urgent in a 70-year-old patient with chronic heart or lung disease, who was a much less satisfactory candidate. Now, with the firm knowledge that current synthetic grafts are extremely durable and infrequently complicated, we are secure in operating on younger patients with smaller aneurysms. If operation becomes necessary in octogenarians, careful anesthetic control and precise cardiac monitoring to prevent underhydration or overhydration have reduced the morbidity in these persons. The greatest cause of perioperative and postoperative morbidity and mortality in aneurysm patients is myocardial infarction. This has led to the current controversy over whether all asymptomatic patients with aneurysm should have coronary angiograms and a prophylactic coronary artery surgical procedure before the aneurysm is resected. There is much to be said for this approach; on the other hand, current statistics do not prove that all patients with asymptomatic carotid bruits should have carotid endarterectomy because the incidence of stroke associated with aneurysm repair is low.

A simple protocol for evaluating any patient older than 50 years seen to have calcium in the abdominal aorta is to obtain a lateral x-ray film. If the anterior wall of the aorta is clearly outlined—even when the posterior aortic wall cannot be seen—measuring the maximum distance from anterior aorta to the vertebral body gives an accurate estimation of the diameter.[1] If the aortic diameter cannot be measured with certainty on lateral x-ray film, then abdominal ultrasonogram or CT scan should be done. If the aorta is greater than 4 cm in outside diameter by any of these measurements, and if after careful medical evaluation the patient has a life expectancy of three to five years, then a prophylactic operation should be seriously considered.

To echo again the findings of Szilagyi and associates,[2] prophylactic surgical repair of abdominal aneu-

rysm by an experienced team at least doubles a patient's life expectancy.

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Mesangial IgA Nephropathies—Steady Progress

ELSEWHERE IN THIS ISSUE is described a case of a patient who had clinical manifestations of a systemic, necrotizing or hypersensitivity vasculitis in a distribution most consistent with Schönlein-Henoch purpura. This diagnosis was established by a renal biopsy specimen, which showed glomerulonephritis with granular deposits of IgA and C3 in the mesangium, associated with mesangial hypercellularity and sclerosis. The patient's renal function failed to improve despite his receiving high-dose steroid therapy, and he subsequently died of other causes. Unfortunately, this course is not uncommon in adults with Schönlein-Henoch purpura who may have rather severe renal disease.[1] Hope that more effective therapy can be developed rests heavily on the premise that a better understanding of the disease mechanisms underlying Schönlein-Henoch purpura and related disorders will lead to less empiric approaches to their treatment. In this syndrome, cautious optimism may be warranted because progress is clearly being made.

Schönlein-Henoch purpura is now viewed as one end of a spectrum of diseases associated with microvascular immune deposits in which IgA is the predominant immunoglobulin seen.[1] The most common of these is IgA nephropathy (Berger's disease) in which clinical manifestations are confined to the kidney. IgA nephropathy is a common cause of "benign" recurrent hematuria, usually presenting immediately following viral upper respiratory tract or gastrointestinal tract infection. There are many reasons to believe that Schönlein-Henoch purpura and IgA nephropathy are probably manifestations of the same disease mechanism, though the causes may differ. Both are characterized by deposition of IgA in the glomerular mesangium and in dermal capillaries of involved and uninvolved skin,[2] and by increases in serum polymeric IgA, IgA-containing immune complexes and IgA-bearing peripheral blood leukocytes.[3-5] The clinical manifestations overlap as well. The occurrence of IgA nephropathy and Schönlein-Henoch purpura has been reported in identical twins,[6] and in patients with IgA nephropathy extrarenal manifestations of Schönlein-Henoch purpura have subsequently developed.[1] Almost certainly studies of the pathogenesis of one of these diseases will apply as well to the other.

How do the mesangial IgA deposits that characterize these diseases develop? The mesangium forms a specialized intercapillary tissue that lies between, and provides structural support to, the filtering capillary loops.[7] Mesangial cells and matrix are separated from the glomerular circulation only by a layer of fenestrated endothelial cells. The mesangium is therefore the principal site of deposition of preformed immune complexes as well as other macromolecular debris that accumulates as a consequence of glomerular sieving function.[7] The mesangial deposits of IgA appear to represent immune complexes containing exogenous antigens and IgA antibody to them.[8] This hypothesis is supported by the increased levels of IgA-containing immune complexes usually present in these diseases when appropriate assays that do not depend on complement fixation are used and the correlation of circulating immune complex levels with clinical manifestations in several patients.[4,9] Mesangial immune complex deposition is directly related to renal immune complex delivery, which is substantially increased if the clearance of immune complexes by the extrarenal mononuclear phagocyte system is impaired.[10,11] As in systemic lupus erythematosus, another renal disease characterized by mesangial immune complex deposits, there is now evidence of impaired mononuclear phagocyte system function in these diseases.[12] Moreover, if the mononuclear phagocyte system imposed by the liver between the portal and systemic circulation is partially bypassed by inducing liver disease or ligating bile ducts, raised serum levels of IgA immune complexes and mesangial IgA deposits result.[13,14] Similar deposits have now been well described in cases of human cirrhosis with portal hypertension and may account for "hepatic glomerulosclerosis."[4] Differences in the capacity of the mononuclear phagocyte system to clear an immune complex load, along with possible differences in size, charge and other factors of circulating immune complexes, may determine why some patients have only mesangial deposits of IgA with mild renal disease while others have more extensive deposits in other systemic capillary beds with the clinical features of Schönlein-Henoch purpura.

If IgA is the antibody component of an immune complex deposited in the mesangium, what antigen is it responding to? This question is almost impossible to answer unless one has some clue regarding what antigens to look for, but clues are emerging. IgA is unique among the immunoglobulins in being derived from two relatively separate sources. Serum IgA is made by plasma cells in spleen and bone marrow, is predominantly monomeric and is 80% to 90% IgA_1, while mucosal IgA is made by plasma cells in the lymphoid systems of the upper respiratory and gastrointestinal tracts, is composed of dimers linked by J chain and contains both IgA_1 and IgA_2 in significant amounts.[15] Initial studies relied heavily on the nature of the IgA subgroups in mesangial deposits to distinguish serum from mucosal IgA and came to differing conclusions.[16,17] However, a consensus is now emerging that the deposits, though

they may contain more IgA_1 than IgA_2, are probably of mucosal origin. Elevated IgA levels are predominantly polymeric,[3] J chain can be detected in the deposits when appropriate depolymerization procedures are used,[18] IgA eluted from the deposits appears to be polymeric[19] and the deposits can bind secretory piece in vitro.[20] Thus the IgA probably represents an antibody response to a mucosal antigenic challenge. This hypothesis is supported by studies showing that mesangial deposits of IgA and J chain can be induced by oral immunization[21] and by the clinical tendency for these diseases to appear, or to be exacerbated by, infections of the upper respiratory and gastrointestinal tracts. The finding that some polysaccharides, which are ubiquitous components of bacterial cell walls and other potential antigens, can elicit a selective IgA response with mesangial deposits of IgA and glomerulonephritis may be another important clue to the nature of the offending antigens.[22] It should be noted that Osler first suggested in 1914[23] that Schönlein-Henoch purpura may be a consequence of an "anaphylactoid" response to some ingested antigens, a postulate that may prove remarkably prophetic.

Identifying the nature and origin of the mesangial immune deposits in these diseases, however, still does not adequately explain why patients in whom such deposits develop also manifest glomerulonephritis and progressive renal failure. Both systemic immune complex formation and mesangial uptake of immune complexes are presumably normal host-defense mechanisms. When preformed immune complexes are deposited in the mesangium, they are normally degraded or taken up by scavenging blood-borne mononuclear cells without much evidence of glomerular injury.[7,24] However, if free antibody combines with antigen already present in the mesangium to produce in situ immune complex formation, more inflammatory change usually occurs.[25] This in situ mechanism of deposit formation may well participate in mediating the more severe proliferative lesions associated with mesangial immune deposits.[26,27] Complement activation is usually required to induce such inflammatory responses, however, and IgA does this poorly at best.

Several recent observations suggest that the mesangium may be more than just a passive recipient of immune reactants delivered to it from the circulation. Mesangial cells may be stimulated by various things, probably including immune complex deposition, to act themselves as immune effector cells in mediating diseases of the glomeruli in which they reside. For example, a subpopulation of these cells bears Ia antigens and thus may present foreign antigens in a genetically restricted fashion to sensitized T lymphocytes, initiating an in situ cell-mediated immune response.[28] Moreover, Lovett and co-workers have shown that mesangial cells by themselves, like neutrophils and macrophages, can release acidic and neutral proteases capable of degrading the type IV collagen of glomerular basement membrane.[29,30] These cells also make a proinflammatory cytokine that closely resembles macrophage interleukin I.[31] The latter is a potent growth factor capable of inducing proliferation of mesangial cells and of other mononuclear cells. Mesangial cells also produce, and probably degrade, several components of the glomerular basal lamina including type IV collagen, fibronectin and laminin, components that accumulate in excess to form the sclerotic lesions so characteristic of progressive glomerular disease.[32,33] Finally, intrinsic mesangial cells resemble smooth muscle cells. They contain actin and myosin, contract in response to angiotensin II and produce vasodilatory prostaglandins.[34,35] These properties may make them important regulators of glomerular microcirculatory dynamics acting to restrict local pressures and flows within individual capillary loops. Interference with this process by mesangial immune injury may result in local glomerular vasodilation with abnormally high pressures and flows, a situation that clearly leads to glomerular sclerosis in other circumstances.[36] Sclerosis, or scarring, is the major cause of glomerular destruction in most progressive renal diseases, including Schönlein-Henoch purpura and IgA nephropathy.

The above is an oversimplified summary of a complex and rapidly evolving area of research, and much more obviously remains to be learned. Fortunately, most patients with mesangial IgA deposits have less severe renal disease than this patient had. It is disheartening that renal involvement in Schönlein-Henoch purpura was first described by Henoch in 1874, yet, more than a century later, we still cannot precisely define the pathogenesis of the disease nor can we treat it effectively. Optimism is encouraged, however, by the fact that most of the observations cited above have been published since 1980, a sign of accelerating progress. Indeed, there is perhaps no better example in renal disease of how the efforts of clinicians, pathologists, immunopathologists, cellular immunologists, cell biologists, biochemists and renal physiologists have interacted to make rapid strides in our understanding of these mesangial immune deposit diseases. Light is visible at the end of the tunnel, which should benefit future patients with these disorders.

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Orders Not to Resuscitate

No task can be more disagreeable for a physician than issuing an explicit instruction that a lifesaving procedure, such as cardiopulmonary resuscitation, be withheld from a patient. Some physicians strongly believe it is unethical to do so; others, while acknowledging such a step may and should be taken, go to great lengths to avoid it. However, in recent years many physicians have honestly acknowledged that in certain cases, it is good and ethical medical practice to consider, discuss and write a "no-code order." The incidence of such orders reported in the articles by Levy and associates and Uhlmann and co-workers in this issue reveals this fact. At the same time, the conditions and criteria that define those certain cases are not entirely clear.

Lee and Cassel review the ethical and legal decisions around do-not-resuscitate (DNR) orders. It is noteworthy that their review stresses that a patient's autonomy should be the basis of such orders, yet Uhlmann records little patient involvement and Levy does not mention it. Lee and Cassel warn about the invidious influence of certain characteristics of patients, yet Uhlmann suggests that social characteristics do appear to carry weight, while Levy reports they do not. Lee and Cassel suggest the importance of a clear clinical diagnosis; Uhlmann reports a high incidence of the diagnosis of neoplastic disease correlated with dementia while Levy notes the presence of a wide and rather unclear set of diagnostic indicia.

Lee and Cassel echo many authorities in recommending that institutions develop clear and explicit policies about DNR orders. Levy does not mention whether his institution had such a policy; Uhlmann states that his did not. Lee and Cassel remark that it may be important that attending physicians write the order, Uhlmann reports that orders are most frequently written by house staff and Levy does not identify the source of the order. It is possible that these differences result from study design. It is more likely that they reflect actual diversity in practice.

The diversity is not merely in practice. It is a disparity between practice and principle. Lee and Cassel state the principles that should be observed in order that the practice of DNR orders be considered ethical. It is, of course, understandable that actual practice does not accord with principle. Persons can and often do disagree with principles or choose to ignore them. In this case, it is probable that the principles are not yet widely known or understood; the disparity arises from ignorance rather than contempt. However, two questions must be asked: Where do such principles come from? How can they be brought to influence practice?

The ethical principles of medicine are not divinely revealed, nor are they issued by any authoritative or amateur body. They grow within the world of medical practice. The seeds of principles are the traditions of medicine, such as "help or at least do no harm." But those seeds are nourished by experience, reflection and honest intercourse between those who engage in and are affected by the practice of medicine. These principles, then, may mature into statements of various sorts, such as oaths, guidelines, directives, reports, comments and essays. Yet these statements are but the outer form of an inner understanding of what constitutes good and ethical practice.

The ethical principles regarding DNR are a recent growth. They, like so much of the ethics of medicine, are rooted in the imperative to help and not to harm:

Just when does the reversal of cardiac or respiratory arrest *help* the patient? When does it do more harm than good? The eager acceptance of CPR in the past two decades disguises the fact that a procedure devised to restore healthy life after a sudden crisis might in some cases provide not health but only a few more days of agonizing life. Slowly, experience has revealed this and studies have confirmed it.

The other essential nutrients for the growth of principles are reflection and honest discussion. These must address the crucial questions: Is continued life always a benefit? Must we employ every energy to forestall death? Who is to designate what sort of living is a benefit? How are we to communicate with each other about these awesome questions? The past two decades have seen the beginnings of this sort of reflection and honest discussion. Academic centers, such as the Kennedy Institute for Bioethics at Georgetown University; centers of research and information, such as the Hastings Center, and government entities, such as the President's Commission for the Study of Ethical Problems in Medicine and in Biomedical and Behavioral Research, have fostered reflection and discussion. Principles have matured in this environment.

The issue behind the ethics of DNR orders is at the very heart of the ethics of medical practice: At what point does the prowess of science and skill become futile? Everyone realizes how difficult it is to make an accurate prognosis; this is not the point. The point is whether the physician is willing to recognize evidences of futility. Everyone knows that many critically ill persons suffer impaired mental capacity; that is not the point. The point is whether the physician is willing to broach the question about the patient's desires while mental capacity yet survives. Everyone knows that "quality of life" is a vague and confusing term. The point is whether physicians are careful in distinguishing their preferences and the prejudices of the society from the values of their patients.

How do principles influence practice? In the first place, many of those reflective persons who engage in honest discussion are physicians. They reflect on their own experiences of caring for critically ill patients and submit their reflections to the view of colleagues and critics alike. They deepen their understanding of the limits of medical intervention and refine their interaction with patients and colleagues about this. Theirs is a principled practice of medicine. However, other practitioners are less reflective. They are not immoral or unethical, but are ethically naive. While competent technically, they are unreflective about the effects of their technical competence. Eloquent scientifically, they are inarticulate morally. They withdraw from honest discussion of ethics or, if they remain, make only rudimentary contributions.

Those physicians who incorporate principles in their practice must communicate with their colleagues who only dimly perceive them. This sort of communication is still sorely lacking. The fact, stated by Uhlmann, that house officers usually make DNR decisions and that attending physicians were "often not involved" is a symptom. Senior physicians have experience; many of them are reflective about their experience. Yet that reflective experience is often not shared. Ward discussions about DNR orders are, in our own experience, perfunctory. It often takes disagreement to raise the level of discussion and, even then, the rise may be in anger, anxiety and authoritarianism rather than in careful analysis. Guidelines are desirable but hardly adequate. The ethics of medical practice is imparted in practice and in the training for practice. It is not peripheral to the clinical decision but central to it. Institutes, conferences and commissions do not create the ethics of practice; they provide a forum for honest discussion. The ethics of practice grow within the reflective experience of practitioners and their patients. The order not to resuscitate is, without doubt, a nodal point for the ethics of practice: through it pass the three essential values of ethical medicine, the autonomy of the patient, the efficacy of intervention and the meaning of human life.

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DRGs and the Art of Medicine

On October 1, 1983, DRGs (Diagnosis Related Groups) became the basis of a system under which the first 1,500 hospitals will receive a set payment per case for their treatment of patients under Medicare. A total of 468 DRGs are recognized and how this new mechanism will operate was spelled out in 138 pages of federal regulations that appeared on September 1. The avowed intent is to change a hospital's incentive to spend more and therefore collect more per case, to an incentive to spend less per case and presumably pocket the difference if it is less than the set payment. It is by no means clear yet whether the DRG payments will be adequate to cover the necessary expenses even under the new incentives, nor is it clear what will happen to the set payments if it turns out that the hospitals are indeed able to achieve any significant cost savings.

In any case it seems certain that this new system will place new stresses upon physicians responsible for the care of Medicare patients while in hospital. Much will depend on which DRG is assigned for a particular hospital admission and much will depend on specifics of the diagnosis and treatment given a patient during a hospital stay. The responsible attending physician will inevitably be in a central position at the interface where economic incentives may conflict with what seems best for a patient. Relationships between personal physicians, medical staffs and hospital administrators, and even with patients and their families, are bound to be affected with much at stake for all concerned.

Physicians throughout history have learned to deal with complex interacting and often conflicting forces

as these affect patients who are ill. This has been part of the art of medicine. In recent years a strong focus on medical science has somewhat overshadowed the art. The art deals with caring for a patient, and with the assessment of inadequate data, probabilities, possibilities, and with external forces that may impinge in one way or another upon a patient. The judgment and skills to do this have long been essential ingredients of the art of medicine. They are acquired by experience, observation and by study.

It would seem that DRGs and the new relationships they will bring about among physicians, hospitals and the elderly patients on Medicare will add yet another dimension to this art of a practicing physician. Somehow the potentially conflicting interests of a patient, the goals of peer review and utilization review, the fiscal needs of the hospital, the scientific imperative (which drives many physicians to do everything possible for every patient) and one's own ethical and professional conscience will all need to be satisfied. Surely to do all of this well and successfully in each case will often be an art.

At this writing only Medicare patients in 1,500 hospitals are involved with DRGs, but the number of hospitals is scheduled to increase, and if the DRG concept is found to work and actually lower hospital costs for patients on Medicare, the principle will no doubt be refined and extended for wider use elsewhere in the health care enterprise. As all this occurs physicians will discover and learn to practice a new dimension in the art of medicine, and this in both the patient and public interest.

MSMW

Case Reports

Successful Treatment of Rocky Mountain 'Spotless' Fever

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IN THE WESTERN United States, a person with a febrile illness who has been exposed to ticks may be infected with *Rickettsia rickettsii, Borrelia* sps or Colorado tick fever virus. In the early stages of a patient's illness, the clinician may not be able to distinguish among the diseases caused by these infectious agents. If clinical findings suggest the possibility of rickettsial infection the physician should institute treatment while tests to define the etiologic agent are being pursued. A case of a patient who was successfully treated for Rocky Mountain "spotless" fever illustrates the importance of early empiric therapy for *R rickettsii.*

Report of a Case

A previously healthy 35-year-old woman from Seattle, Washington, went hiking in Idaho in early July 1982. She was exposed to numerous ticks, but noted no definite tick bites. Four days after her first tick exposure, a high fever suddenly developed that was associated with a frontal headache, myalgia and general malaise. She was seen by Dr Royal A. McClure at the Mollie Scott Clinic in Sun Valley, Idaho, where results of a physical examination were entirely normal except for an oral temperature of 39.1°C (102.4°F). Initial laboratory findings included a hematocrit of 42%; leukocyte count, 7,400 per μl, with 83% polymorphonuclear leukocytes and 5% band forms. Serum electrolyte, blood sugar and blood urea nitrogen values were normal, but the serum aspartate amino transferase value was elevated to 101 IU per liter. The woman was admitted to hospital and on the second day her temperature rose to 40.2°C (104.4°F) despite aspirin and acetaminophen administration. Eight cultures of blood specimens drawn during the first 48 hours of her hospital course were negative for any pathogens and a chest roentgenogram showed no abnormalities. On the third hospital day, the patient's temperature dropped to 37.3°C (99°F) and her headache and other symptoms resolved. On the following day, however, her fever returned along with headache, nausea and myalgia; she also had one episode of diarrhea. In addition, her urine was "dark" and tested positive for hemoglobin. On the fourth day in hospital, the hematocrit was 30% and the leukocyte count was 5,700 per μl with 60% polymorphonuclear leukocytes and 31% band forms; the platelet count was 140,000 per μl. No abnormalities were found on repeat physical examination and no skin rash was seen. Over the next two days, the patient's temperature remained elevated at 38.3°C (101°F) and the hematocrit values remained stable. A repeat serum aspartate amino transferase test showed a value of 194 IU per liter. At this time, six days after the onset of illness, the patient was started on a regimen of tetracycline (500 mg by mouth four times a day) because of a possibile diagnosis of Rocky Mountain "spotless" fever.

The patient returned to Seattle and three days later was admitted to University Hospital because of continued fever, headache, nausea, myalgia and general malaise. She had been taking tetracycline faithfully for three days. On initial physical examination, vital signs were as follows: blood pressure 114/66 mm of mercury, temperature 38.4°C (101.1°F) and pulse 76 per minute. No skin rash was present and results of physical examination were entirely normal.

Laboratory data included a hematocrit of 32%; leukocyte count of 13,000 per μl, with no band forms in the differential, and normal serum electrolyte, blood urea nitrogen, blood glucose and creatinine values. Tests revealed elevated values for serum aspartate amino transferase (143 IU per liter), serum alanine amino transferase (170 IU per liter) and alkaline phosphatase (234 IU per liter). Analysis of urine and chest x-ray studies showed no abnormalities. There was no evidence of past or present hepatitis A or B infection. Tetracycline therapy was continued at a dose of 500 mg by mouth four times a day for the next five days. The patient's symptoms slowly resolved during this period and, at the time of discharge home, she had no fever.

During the patient's hospital course, a sample of clotted blood was sent to the Vector Borne Diseases Division, Bureau of Laboratories, Center for Disease Control (CDC) in Fort Collins, Colorado, for culture for Colorado tick fever virus. The culture yielded no organisms. Blood specimens for serologic studies were obtained at the time of admission to University Hospital (eight days into the illness) and again three weeks later. The specimens were analyzed by the CDC laboratories at Fort Collins, Colorado, using the neutralization test, and no evidence of Colorado tick fever was found. The specimens were also sent to the Centers for Disease Control laboratories in Atlanta for detec-

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TABLE 1.—*Clinical Features of Three Tick-borne Infections Found in the Western United States*

	Rocky Mountain Spotted Fever	*Relapsing Fever*	*Colorado Tick Fever*
Agent	*Rickettsia rickettsii*	*Borrelia* sps	RNA virus
Tick vector	*Dermacentor* sps	*Ornithodoros* sps	*Dermacentor* sps
Incubation period	4 to 8 days	3 to 7 days	4 to 5 days
Onset of symptoms*	Sudden	Sudden	Sudden (50% of cases have biphasic course)
Rash			
At onset of illness	No	No	No
At day 4	Typical rash see in approximately 90% of patients†	Maculopapular rash or petechiae may occur	No (5% to 10% of patients may have a macular rash)
Respiratory tract findings	Possible	Possible	Rare
Splenomegaly	Possible (50%)	Possible (50%)	Rare
Hepatitis	Possible	Possible	Rare
Edema	Possible	No	No
Encephalopathy	Possible	Rare	Rare
Laboratory findings	Hyponatremia, anemia, thrombocytopenia, disseminated intravascular coagulation	Thrombocytopenia	Leukopenia

*Fever, headache, myalgia and malaise occur in most patients. Some patients may also experience abdominal pain, nausea, vomiting or diarrhea.
†Rash may not appear in patients who receive early treatment.

tion of rickettsial antigens by indirect fluorescent antibody and complement fixation techniques. By indirect fluorescent antibody assay, a rise in titer for Rocky Mountain spotted fever from 1:64 in the acute serum to 1:512 in the convalescent specimen was reported. These results were interpreted as indicating acute infection with Rocky Mountain spotted fever. The CDC does not currently use the complement fixation technique in serologic studies to diagnose Rocky Mountain spotted fever. A *Proteus* agglutination test done in our laboratory on a specimen taken during convalescence showed a strong reaction with OX-19 (1:160), a weak reaction with OX-2 (1:20) and no reaction with OX-K.

The patient has been seen in follow-up visits twice since her hospital stay. Liver function test values returned to normal and the patient felt entirely well one month after leaving the hospital. She remained well and had no evidence of relapsing infection when she was examined during a clinic visit five months later.

Discussion

The widely accepted terms for diseases associated with tick-borne infections are misleading. Rocky Mountain spotted fever occurs more frequently in the eastern United States than in the Rocky Mountain area,[1,2] and the typical spotted rash may be absent.[1,3,4] Colorado tick fever has been reported in eight western states in addition to Colorado[5] and relapsing fever does not necessarily relapse.[6] A history of tick bite suggests the possibility of one of these infections, but 50% of patients may not report a tick bite and as many as 10% to 20% of patients may not even report tick exposure.[1,5,6]

Clinical findings may help a clinician distinguish among the tick-borne infections (Table 1). However, these diseases often are clinically similar during the first week of illness. Careful microscopic examination of a blood smear can provide a rapid diagnosis of infection with *Borrelia* sps,[6] but there are no rapid laboratory tests available for promptly diagnosing Colorado tick fever or *Rickettsia rickettsii* infection. Fluorescent antibody staining of erythrocytes may allow detection of Colorado tick fever virus[5] and fluorescent antibody staining of a specimen from a skin lesion can provide a rapid diagnosis of Rocky Mountain spotted fever.[7,8] However, these techniques are only available in a few laboratories. The *Proteus* agglutination test (Weil-Felix reaction) is not a reliable method for early diagnosis of *R rickettsii* infection.[9] Multiple organ system involvement with clinical findings of coagulation abnormalities, hepatitis, lower respiratory tract findings, encephalopathy or renal failure may suggest the diagnosis of Rocky Mountain spotted fever in the later stages of a patient's illness.[10-14]

As many as 86% of patients with Rocky Mountain spotted fever may not have the typical spotted rash within the first four days of the onset of illness[4] and in a few patients a skin rash[1] may never develop. Several investigators have suggested that early antibiotic treatment of Rocky Mountain spotted fever can delay or prevent the rash. When the characteristic rash does not develop in the first few days of a patient's illness, delay in diagnosis and treatment results. Five recent cases of fatal Rocky Mountain "spotless" fever have been reported in patients in whom the diagnosis was missed because of the absence of typical skin findings in the first five to seven days of illness.[3,4]

Fever and systemic symptoms did not resolve in our patient until she had received tetracycline for seven days. The delayed response to tetracycline and the biphasic nature of the initial symptoms suggested the possibility of Colorado tick fever[5] or of another viral infection. However, a slow response to tetracycline has been recognized in patients with *R rickettsii* infection,

though the biphasic nature of the onset of illness is unusual for this infection.

Our patient was successfully treated for Rocky Mountain "spotless" fever, though the diagnosis was not proved until the results of serologic studies became available six weeks after stay in hospital. The eight-day course of tetracycline was administered because of the history of tick exposure and the sudden onset of high fever, headache, myalgia, mild liver function abnormalities and the possibility of a hemolytic episode. In a patient in whom the sudden onset of a severe febrile illness develops within two weeks of possible tick exposure, empiric use of tetracycline may be indicated. Although the presence of the typical rash of Rocky Mountain spotted fever can be helpful in the differential diagnosis of tick-borne fever, the absence of cutaneous findings may be consistent with multiple causes of tick-borne fever, including *R rickettsii*.

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Bordetella bronchiseptica Bacteremia

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Bordetella bronchiseptica, a Gram-negative nonfermentative bacillus, has been extensively studied as a veterinary pathogen and in animal models of bacterial superinfection following viral respiratory tract disease.[1] There are few reports of disease in humans caused by this organism. We describe the case of a patient in whom *B bronchiseptica* bacteremia developed in hospital and persisted for ten days, despite treatment with antimicrobial agents to which the organism was susceptible in vitro. The clinical course and autopsy findings in this patient are described and previously reported cases of *B bronchiseptica* infection in humans are summarized.

Report of a Case

The patient, a 70-year-old black man, was admitted to the Veterans Administration Medical Center because of weight loss, anorexia and intermittent abdominal pain for two months. There was no history of respiratory tract infection, contact with animals or previous illness. On physical examination he was noted to have icterus and an enlarged liver; stool specimens were guaiac positive. A chest roentgenogram showed a subtle density in the right midlung field. Liver function tests showed an aspartate aminotransferase (AST, formerly SGOT) level of 200 IU and an alkaline phosphatase value of 980 IU per liter. The total bilirubin level was 7.7 mg per dl, of which 4.3 mg per dl was direct reacting. The peripheral leukocyte count was 4,500 per μl, the hemoglobin 13.3 grams per dl and the hematocrit 37.9%.

Metastatic cancer was suspected, and the following special studies were done: barium enema, liver-spleen radioisotope scan, abdominal ultrasound, endoscopic retrograde cholangiopancreatography, whole lung tomography and bronchoscopy. None of the above showed abnormalities. Serologic tests for hepatitis A and B viruses, α-fetoprotein, antimitochondrial antibody, cytomegalovirus, Epstein-Barr virus, toxoplasma and Q fever were negative. Results of serum immunoglobulins and a serum protein electrophoresis were normal. Contrast studies of the gastrointestinal tract showed a small duodenal ulcer, and treatment with cimetidine was begun on the 12th hospital day.

An elevated temperature was noted on the 18th hospital day, and one of two blood cultures done grew a Gram-negative bacillus from the aerobic bottle after 24 hours. Three additional blood cultures were taken and, again, one of three aerobic bottles was positive. Therapy that had been initiated with a "third-generation" cephalosporin (cefoperazone sodium) was changed to gentamicin sulfate, 1.5 mg per kg of body weight every eight hours, when antibiotic susceptibility studies showed that the organism was resistant to

(Katzenstein DA, Ciofalo L, Jordan MC: *Bordetella bronchiseptica* bacteremia. West J Med 1984 Jan; 140:96-98.)

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cefoperazone. The Gram-negative bacilli from both positive blood cultures were identified as *Bordetella bronchiseptica* by selective biochemical and negative fermentation reactions. Continued fever prompted the addition of ampicillin and clindamycin to the antibiotic regimen; however, blood cultures continued to grow only *B bronchiseptica* (Figure 1). An increasing serum bilirubin concentration and a falling hematocrit were noted on the 24th hospital day and, despite multiple transfusions, the patient suffered a cardiopulmonary arrest. The hematocrit was 15% and, despite continued transfusion, intubation and mechanical ventilation, the patient died on the 29th hospital day. Blood cultures done before death continued to grow *B bronchiseptica.*

Autopsy Findings

At autopsy a ruptured spleen was found, to which was attached a well-circumscribed hematoma, equivalent to 600 ml of blood. The intestines and the heart and lungs were free of significant gross lesions. A thickened pleural scar overlying the right lung accounted for the density appearing on an x-ray film of the chest. The liver weighed 1,500 grams and had a smooth surface. The intrahepatic and extrahepatic ducts were normal in caliber. The biliary system was free of calculi, and the bile itself was unremarkable.

Microscopic examination of the spleen showed massive numbers of sickled erythrocytes in association with infarcted splenic tissue. A fragment of splenic capsule and attached pericapsular fat showed extensive infiltration by polymorphonuclear leukocytes. An adjacent minor splenic artery exhibited occlusion of the lumen with dissection of the muscular wall and polymorphonuclear leukocytic invasion peripherally. Liver sections showed fibrosis of portal areas with mild reduplication of bile ductules and prominent mononuclear cell infiltration. Examination of sinusoidal spaces showed numerous sickled erythrocytes. Kupffer's cells were prominent, and erythrophagocytosis was visible. Postmortem culture of liver, spleen and blood specimens grew *Bordetella bronchiseptica.*

Microbiology

The Gram-negative coccobacillus initially isolated from blood cultures was identified as *B bronchiseptica* by the API-20E system (API Analytab Products, Ayerst Laboratories, Plainville, NY). Characteristic observations included positive citrate and rapid conversion of urea. The organism was motile and showed one to two polar flagella by Bacto flagella staining (Difco Laboratories, Detroit, Mich) and was noted to be peritrichous by a shadowing technique on unstained organisms using electron microscopy. Identification of the organism was confirmed by the Centers for Disease Control in Atlanta by means of differential biochemistry, growth characteristics on media and serologically.

Susceptibility testing showed resistance of the organism to ampicillin, cephalothin, chloramphenicol, carbenicillin and amikacin. Growth of the organism was inhibited in vitro by achievable concentrations of gentamicin, tetracycline and trimethoprim/sulfamethoxazole (Table 1). One hour after the patient was

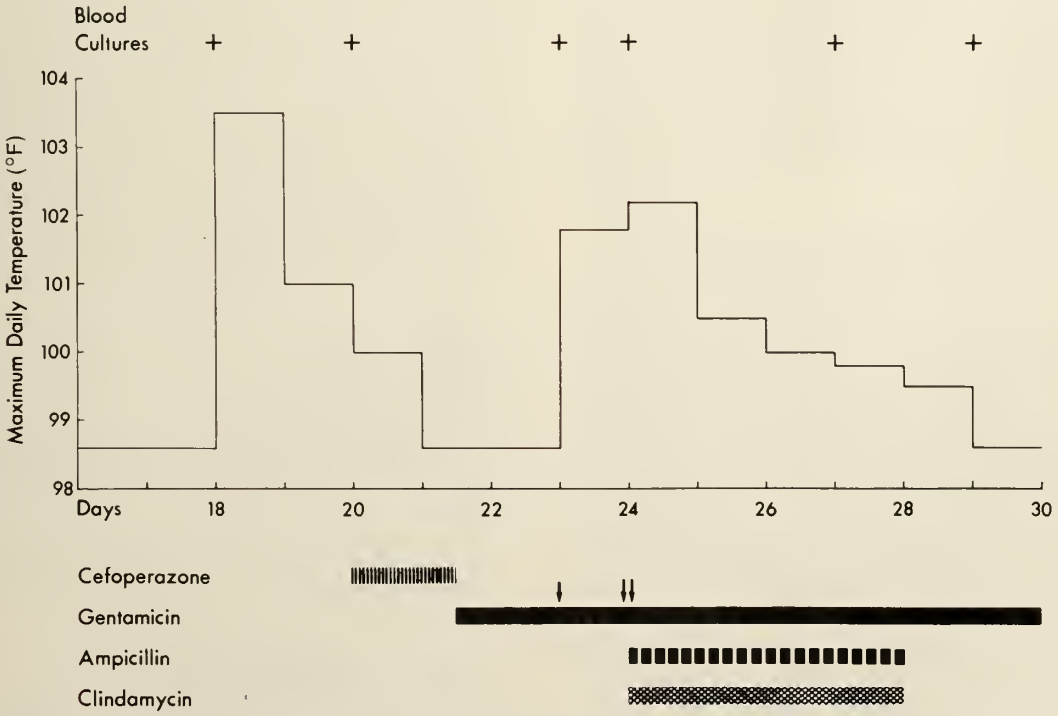

Figure 1.—Maximum daily temperature and time of positive blood cultures and antibiotic therapy from the 18th through the 29th day in hospital. ↓=gentamicin sulfate concentration: premedication level 1.0 μg per ml, postmedication level 4.8 μg per ml; ↓↓=serum bactericidal activity measured: premedication 1:16, postmedication 1:64.

TABLE 1.—*Minimal Inhibitory Concentration (MIC) Testing of* Bordetella bronchiseptica

Antibiotic	*MIC*	*Antibiotic*	*MIC*
Ampicillin	> 16 μg/ml	Amikacin	24 μg/ml
Cephalothin	> 64 μg/ml	Cefamandole nafate	> 64 μg/ml
Gentamicin sulfate	2 μg/ml	Cefoxitin sodium	> 64 μg/ml
Tetracycline	8 μg/ml	Colistin sulfate	4 μg/ml
Carbenicillin	>512 μg/ml	Nitrofurantoin	> 64 μg/ml
Chloramphenicol	> 32 μg/ml	Trimethoprim/sulfamethoxazole	2/38 μg/ml
Tobramycin	4 μg/ml	Clindamycin	> 64 μg/ml

given a dose of gentamicin, his serum was bactericidal for the *B bronchiseptica* at a dilution of or greater than 1:8 when an inoculum of 10^5 organisms per milliliter was used.

Comments

B bronchiseptica is infrequently isolated from human clinical specimens and is even less often a cause of disease. Two recent surveys of nonfermentative Gram-negative organisms address the issue of pathogenicity. Pedersen and co-workers speciated 565 nonfermenting Gram-negative bacilli isolated in a two-year period:[2] 12 were *B bronchiseptica,* all were isolated from sputum samples and none were associated with disease. In a more recent study, Gardner and associates identified 18 of 184 nonfermenters isolated from specimens in Boston as *B bronchiseptica.*[3] In all, 16 were found in sputum specimens, one in urine and the other, in one case discussed later, in blood. Thus, it is unusual to identify *B bronchiseptica* in clinical specimens and neither has prolonged bacteremia been reported previously.

In all, we found seven cases of human infection reported in the literature. The organism was first characterized by McGowan[4] who described a laboratory epidemic of tracheobronchitis and pneumonia in dogs, rabbits and guinea pigs. *B bronchiseptica* was isolated in pure culture from the nasopharynx of a laboratory worker with a history of chronic catarrh. In 1926 Brown[5] reported a case of typical whooping cough in a child with a sick pet rabbit and *B bronchiseptica* was grown in specimens from the nasopharynx of both the child and the rabbit. Kristensen and Lantrop[6] in Denmark and Krepler and Flamm[7] in Germany have each reported the case of a respiratory tract infection caused by *B bronchiseptica.* Chang and colleagues[8] described the case of a child in whom posttraumatic meningitis with *B bronchiseptica* developed. Finally, two cases of bacteremia and lethal infection have been described. Gardner and co-workers[3] discuss the case of an elderly immunosuppressed man in whom a terminal bacteremia developed with both *B bronchiseptica* and *Streptococcus pneumoniae* while he was receiving corticosteroids and azathioprine. Recently Ghosh and Tranter[9] reported isolating *B bronchiseptica* from specimens of blood and tracheal aspirate from a malnourished alcoholic patient with a fatal aspiration pneumonia.

In our patient, nosocomial infection resulted in a prolonged bacteremia without an antecedent pulmonary infection, contact with an animal or an apparent port of entry. Although he was not obviously immunosuppressed, he may have been particularly susceptible to this unusual infection for two reasons. First, he entered the hospital with cholestatic liver disease that eluded classification despite intensive clinical and postmortem study. Second, the patient probably had a sickling hemoglobinopathy, most likely hemoglobin AS (sickle cell trait). Unfortunately, this was not suspected during life, and a hemoglobin electrophoresis was not done. However, the pathologic findings were consistent with sickle cell trait. Intravascular sickling leading to splenic infarction has been described in up to 20% of patients with sickle cell trait subject to the stress of serious illness.[10] Sickled hemoglobin probably caused the multiple splenic infarctions that led to rupture of the spleen. Virtual destruction of the spleen may have further diminished his ability to remove bacteria from the blood and provided a nidus for continued bacteremia.

This case shows that *Bordetella bronchiseptica* is a human pathogen that may cause prolonged lethal bacteremia. Cultures of blood specimens taken before and during appropriate antibiotic therapy were positive, albeit usually only one of two or three sets grew *B bronchiseptica.* This is consistent with continuous, low-level bacteremia as in an intravascular infection or undrained abscess. Multiple splenic infarctions and splenic arteritis may have provided a site for microabscesses with access to the bloodstream. Liver disease and a sickle cell hemoglobinopathy in this patient may have resulted in further inability to clear bacteremia.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Normotensive Pheochromocytoma

To THE EDITOR: In the recent article by Kirby and co-workers[1] a case of pheochromocytoma is described in detail and the expanding spectrum of paraneoplastic syndromes associated with this tumor is discussed. Of particular interest in the case was the presence of normotension in a disease usually characterized by hypertension. The authors provide possible pharmacological bases for this phenomenon. They suggest that tissue receptors may become tolerant to catecholamines or that the concomitant production of dopamine and dopa by the tumor may modulate the hypertensive effects of norepinephrine. While I do not disagree with this explanation, I intend to present other potential factors that may account for this phenomenon and possibly other paraneoplastic syndromes associated with this tumor.

One of the richest sources of endogenous opioids (endorphins/enkephalins) is the adrenal medulla, which contains high concentrations of opioid peptides derived from proenkephalin (for enkephalins) and proopiomelanocortin (for endorphin).[2] Opioid peptides are stored in chromaffin cells and are released together with adrenalin during stress. Human pheochromocytomas contain high levels of methionine-enkephalin and leucine-enkephalin immunoreactivity, often several times higher than concentrations reported for normal adrenal medulla.[3] The opioid peptides have hypotensive effects in anesthesized laboratory animals and may play a role in the pathogenesis of shock.[4] The opioid peptides have a variety of other biological effects; these include dopamine-potentiating, analgesic, behavioral, and immunomodulatory properties.[5] It is plausible that some of the paraneoplastic syndromes associated with pheochromocytoma and other neuroendocrine tumors are related to the excess production of these opioid peptides. Plasma levels of endorphins or enkephalins were not reported by Kirby and her associates; however, the measurement of these substances may be important in correlating certain clinical phenomena with the pharmacology of tumors.

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Tick Removal

To THE EDITOR: The interesting article on ectoparasites by Pien and Grekin[1] stimulated me to share my experience in trying to control ticks and fleas. A simple and safe method of tick removal is to coat the tick with petroleum jelly (such as Vaseline), wait ten minutes and then gently remove the tick with forceps, grasping it very close to the skin of patient or pet. The tick can be removed intact without problems associated with application of strong chemicals or burning. In addition, petroleum jelly based ointments are readily available in most homes.

Fleas have become increasingly troublesome as flea control pet collars have lost effectiveness. DDT powder, recommended by the authors, is not available in the United States. Many people find malathion and pyrethrins unacceptable because of allergenicity. An alternative is 5% carbaryl powder. While there are also objections to carbaryl, it is reasonably effective and inexpensive.

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Relation Between Surgical Volume and Postoperative Wound Infection

To THE EDITOR: In 1981 Farber and co-workers[1] reported that for appendectomy, cholecystectomy and herniorrhaphy the fewer operations done annually in a given institution, the greater the incidence of postoperative wound infection. They concluded that their study "provides additional data clearly demonstrating that morbidity is higher in hospitals performing very little surgery." In discussing these findings, Richards[2] asked whether "the data in this study would have more value if the authors had also compared differences in surgical volume and incidence of wound infections *per physician* and then contrasted these differences with hospital size." Farber and associates[3] agreed "that the data in our

study would have been more meaningful if the infection rate had been given for individual surgeons."

We designed a prospective study to examine the postoperative wound infection rate for one board certified general surgeon (J.M.G.) operating in a 36-bed community hospital in rural Utah (Tooele Valley Hospital) in which fewer than 650 operations are carried out annually. The study group consisted of 135 consecutive patients who underwent emergency appendectomy, emergency or elective biliary tract surgical procedures, or emergency or elective inguinal herniorrhaphy between July 1, 1981, and June 30, 1983. The operative techniques, methods of antisepsis and usage of antibiotic prophylaxis against wound infection were those generally accepted by the surgical community and may be found in any of the current textbooks of surgery.[4,5] All wounds were examined by the surgeon or the hospital's infection control officer (A.B.S.), or both, daily during the hospital stay and approximately weekly thereafter for six weeks after operation. Wound infection was defined as the presence of pus at the incision or drain site.

Of 41 emergency appendectomy operations carried out, there was one postoperative wound infection (incidence, 2.4%). Of 39 biliary tract operations and 55 inguinal hernia repairs, there were no postoperative wound infections. The incidence of postoperative wound infection for the entire group of 135 patients was 0.74%.

Luft and co-workers[6] have also argued for regionalization of surgical procedures; however, they emphasize that "operations are performed and patients are cared for not by hospitals but by surgeons. . . . The poor outcomes in a specific hospital may be the result of the good outcomes of one well qualified surgeon being swamped by the poor outcomes of several 'occasional' surgeons." From the data presented it would seem that individual surgeons, by using standard technique and generally accepted means of preventing postoperative wound infection can achieve good results in a small, rural hospital.

There has been a change recently in the geographic distribution of board certified surgeons toward smaller, more rural communities.[7] This trend can only result in improved surgical care in rural settings. When seeking surgical services, the dictum should be to examine the credentials and record of the individual surgeon and not the size or location of the hospital.

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The opinions and assertions contained herein are the personal view of the authors and are not to be construed as official policy of the US Department of the Navy or Department of Defense.

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Rattlesnake Bites

To the Editor: A dangerous policy is to make an authoritative statement on the basis of a small, retrospective case review, especially when details of hospital progress and outcome are incomplete. Such is the case with Butner's article regarding rattlesnake envenomation in northern California.[1]

If this article had been published as a review of symptomatology and the current therapy recommended by Russell[2] and other noted authorities in the field, the statements would be acceptable. Unfortunately, the author makes a recommendation for antivenin therapy not based on personal clinical experience, but on the treatment rendered by various, probably inexperienced, physicians in many hospitals over 17 years. There is no indication of the patients' length of stay, cost of therapy or outcome except for zero mortality and one case of necrosis.

The problem is that the author has recommended minimal doses of antidote for a serious poisoning. The venom of *Crotalus viridis* (of either the subspecies *oreganus* or *helleri*) is highly toxic, exceeded in LD^{50} only by *Crotalus scutulatus* (Mojave green rattlesnake).[2,3] A second problem is due to the polyvalent antivenin itself. The antibody titer of this product to the proteins of *Crotalus viridis* venom may not be high. The antivenin is produced by immunization of horses with pit viper venoms other than *Crotalus viridis,* then standardized in mice rather than humans. The venom of all US pit vipers varies considerably in protein size and content.[2] The currently available antivenin clinically is not very potent in neutralizing envenomation by northern Pacific rattlesnakes.

We have treated 825 pit viper envenomations at this medical center, 80 in the past three years. Our experience indicates that administration or two or three vials of antivenin would be a disastrously small amount, especially in children. The fact that the patients in the retrospective review survived does not indicate that the treatment was adequate. These patients may have been in hospital or incapacitated for weeks.

Using the vast experience of Dr Findlay Russell, we have devised a simple initial classification and treatment regimen for bites of *Crotalus viridis* species. While a number of factors influence the amount of venom the snake releases during a bite, clinical and laboratory findings appear to be the best basis for grading severity at the time the patient is first seen.

We grade envenomation as follows:

- Minimal: Local swelling
  Paresthesias
  No laboratory changes

- Moderate: Swelling which progresses beyond the site of the bite
  Ecchymosis
  Laboratory changes, such as decrease in platelets or fibrinogen, or prolonged bleeding time
- Severe: Pronounced, rapidly progressing local reaction
  Severe system reaction, such as hypotension, hemorrhage

We then administer the initial dose of antivenin intravenously as follows:

- Minimal: 5 vials
- Moderate: 10 vials
- Severe: 15 vials

This is diluted in 0.5N saline in a volume compatible with the patient's size and administered as rapidly as tolerated, usually over two hours. We never use less than five vials. The response is much greater and more complete. The progress of edema then is noted and administration of antivenin is repeated in five to ten vial increments every hour until the swelling stops and the patient becomes asymptomatic. It should be noted that the dose for children and small persons should be increased by 50%. Children tolerate pit viper envenomation poorly.

With this regimen, almost all of our patients recover promptly and may be discharged on the third or fourth day after admission.

The remainder of Dr Butner's recommendations are satisfactory. We have not used surgical therapy (fasciotomy) in any of our 825 cases and have had excellent results. I hope that any physician contemplating incising an envenomated patient will read the article by Garfin and co-workers[3] and also will consider the coagulation problems associated with pit viper venom.

Finally, I wish to repeat that authoritative statements on serious problems should not be associated with small retrospective studies.

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Dr Butner Responds

To the Editor: I am gratified that Dr Wingert has recognized the importance of reevaluating the treatment of rattlesnake bites. However, it is evident to me that he has confused two common subspecies of rattlesnakes found in California: the *Crotalus viridis oreganus* (Cvo, northern Pacific rattlesnake) found in northern California, Oregon and Washington and the *Crotalus viridis helleri* (Cvh, southern Pacific rattlesnake) found in a limited part of southern California.[1,2] I have no argument with the antivenin doses established for the "highly toxic" Cvh.[2,3] In a clinical setting the Cvo appears to be less poisonous than Cvh based on the favorable patient response to lower antivenin doses in the former.[4]

Hospital stays varied, and as expected, increased with severity. In a total of 47 patients the average stay was as follows: grade 0, one day; grade I, three days; grade II, four days; grade III, six days. Note, there were no grade IV patients. Treatment should be based on the virulence of local reptiles and not on less specific recommendations based on national studies.

In my opinion the gradation of toxicity used by Dr Wingert does not lend itself to a sensitive adjustment of antivenin dosage as the toxic state progresses.

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Medical Staff Conference on Osteoporosis

To the Editor: I have just finished reading the Medical Staff Conference on osteoporosis in the July and August 1983 issues. As a family practitioner with many elderly patients I am very interested in this subject from the practical clinical point of view.

While part I of the conference was very informative in its discussion of the new advanced radiologic techniques used to quantify osteoporosis, I was disappointed that there was no sensitive discussion of the practical clinical applicability (or lack of it) for these techniques. Dr Gordan in part II praises the "computed tomographic scanning technique [as] a distinguished contribution to the early detection of postmenopausal bone loss" and notes it is possible to use it "to detect insidious, painless bone loss in persons years before fractures occur." Nonetheless, he also reports the dramatic facts that American women "can expect to live 40% of their lives after menopause" (32 years) and "by age 70, these [susceptible] women have on the average lost 50% of their peripheral cortical bone mass." Later he states that "women in their 80s have a 40% chance of having sustained one or more hip fractures" (not to mention vertebral and wrist fractures). In view of this virtual epidemic of morbidity and mortality due to the complications of osteoporosis and the effectiveness of preventive measures, I was disappointed that neither the members of the Department of Medicine at the University of California, San Francisco nor the editor of The Western Journal

of Medicine chose to distinguish between the use of this expensive technology in clinical research and its role in day-to-day practice.

In this era of cost consciousness in medicine this is a valid and lively issue of significance in our community. About a year ago one local hospital started to advertise the availability of a nuclear medicine bone densitometry technique to assess osteoporosis which cost *only* $80 and recently another publicized a computed tomography technique with dramatic pictures similar to those published in your article recommending an "optimum plan would be . . . a baseline scan (at surgical bilateral oophorectomy, menopause or within 5 years of menopause) . . . followed by scans at 6 to 12 month intervals to determine desirability of therapy." Later on scans every 1 or 2 years should be sufficient to evaluate effectiveness of therapy." The charge for each scan is $168 ("total hospital and professional components").

Frankly, in the context of clinical practice and high epidemiologic risk this technology and expense seems to be largely unnecessary. Patients can be evaluated according to their demographic risk profile and clinical presentation and treated empirically. Even Dr Gordan goes so far as to suggest such an inexpensive and practical (if nonremunerative) instrument as a tape measure to document the progress of the disease.

Advanced radiologic techniques clearly have their real utility in clinical research establishing the natural history of primary osteoporosis and evaluating preventive and therapeutic regimens (as in the dose-response effect of estrogen). Probably because of existing uncertainties Dr Gordan did not greatly explore the clinical significance of the various oral calcium salts, exercise, the use of vitamin D analogues, of androgens and of fluoride in the prevention and treatment of osteoporosis. Undoubtedly CT scan bone mineral analysis will contribute greatly to the resolution of these controversies through clinical research, and further specify optimal prevention and treatment programs. Meanwhile I think the academic medical center and the journal have a responsibility to be sensitive to the cost issue and convey appropriate reservations instead of appearing to contribute to the marketing efforts of local hospitals and radiology groups.

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* * *

Dr Gordan Responds

To the Editor: I am very grateful to Dr Jeoffry B. Gordon for his interest in postmenopausal osteoporosis and for raising important points where there may be misunderstanding. He is certainly correct to note that this is now an epidemic for which we have effective preventive measures. Bone mass measurements have revolutionized the subject not because they are essential to detect early bone loss before fractures, but because they have convinced medical and scientific audiences that (1) almost all white-, yellow- and brown-skinned women lose a significant amount of bone after loss of ovarian function and (2) they permit rapid evaluation of the efficacy of preventive measures. Two years ago, we did not know how much estrogen was needed for prophylaxis but now we know from our own study that 0.6 mg conjugated estrogens prevents bone loss in five of six women, and from Christiansen's study that 2 mg estradiol is equally effective. I feel particularly fortunate that our experimental studies include bone mass measurements so that we can identify the one of six women not protected by the 0.6 mg dose. When we increased the dose to 1.25 mg we found, a year later, that much of the lost bone had been regained.

It is now possible to measure *separately,* peripheral or axial bone, cortical or trabecular bone, and integral bone in the spine. While the last is the cheapest method for the spine, it is less sensitive for my purposes than measurement of vertebral spongiosa by quantitative computed tomography (QCT). Unfortunately, dual-beam absorptiometry (DPA) includes not only the rapidly mobilized spongiosa but also the cortex (which changes more slowly) as well as osteophytes, vascular calcification, endplate sclerosis, articular facet hypertrophy and vertebral compressions, all of which increase at the very time when spongiosa is disappearing The tape measure *is* useful, not for early bone loss, but for detecting loss of height due to compression fractures, a complication which occurs a decade later.

As an endocrinologist my preference, of course, is for hormone replacement therapy. If a patient has a thyroid deficiency, I give thyroid hormone; for estrogen deficiency I prefer estrogen replacement, whenever this is feasible. Large dose calcium administration has been reported by others to *retard,* but not prevent postmenopausal bone loss but our present data with 1,500 mg per day (unpublished) are most disappointing; almost all of these women lost a great deal of bone. While we oppose immobilization, we know that exercise alone will not prevent bone loss due to estrogen deficiency, as recently exemplified by young runners with amenorrhea who lose bone and sustain fractures while running 40 miles per week. The uselessness of vitamin D analogs, and indeed their harmfulness, has been well shown by Christiansen and co-workers, and is illustrated in Figure 3 of our article. Fluorosis is characterized by increased bone density but I am not willing to recommend large doses of fluoride at the present time. Fluorosis is a painful disease with arthritis and peritendonitis calcarea and fluorotic bone is abnormal. Furthermore, large doses of fluoride combine with hydrochloric acid in the stomach to produce hematemesis and anemia. In my view, estrogen replacement therapy is both more appropriate and safer for postmenopausal women, unless contraindicated.

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To the Editor: The July 1983 Medical Staff Conference "Osteoporosis: Part I. Advanced Radiologic Assessment Using Quantitative Computed Tomogra-

phy," inadequately describes the utility of a competing diagnostic method. Dual photon absorptiometry (DPA) provides lumbar spine mineral measurements with 2% precision in our experience. The determination is now almost wholly automated and does not depend on a physicist for data processing. Accuracy is 3% for ashed vertebral specimens.[1] Maximum patient radiation dosimetry is 15 millirads to the area measured, depending on the age of the gadolinium-153 radioactive source used, compared to a minimum of about 20 times this dose for single energy computed tomographic measurement.[2,3] For nearly comparable accuracy to DPA, quantitative computed tomography (QCT) must be done at dual energy ranges at much larger radiation exposures and with degradation of precision. Contrary to Dr Genant's comments, DPA has been available since June 1982 at our private practice laboratory next door to the University of California Medical Center, San Francisco, where we have now done approximately 750 patient studies, and the procedure is available at approximately 50 locations in the United States and abroad, about the same number of installations as Dr Genant's QCT approach. There are two commercial instruments for sale now and two additional firms are developing instruments. The procedure is rapidly becoming more generally available.

I believe discussion of the utility of the two methods will devolve upon their relative precision in following change in individual patients, their accuracy, procedure cost, radiation dosimetry (although QCT's larger dose is well within the scope of other diagnostic exposures), and whether DPA measurement of all mineral in the field of view versus QCT measurement of trabecular mineral constitutes a significant handicap in following individual patients. Not all QCT installations will succeed in offering the elegant attention to detail in QCT analysis offered by Dr Cann at the University of California, and are therefore unlikely to attain his precision. The automated processing offered by one manufacturer already constitutes a major advantage of DPA over QCT.[4] QCT does have significant accuracy and precision problems.[5] I believe that while QCT may provide elegant data on trabecular bone mineral change when group data are averaged, DPA will be the procedure of choice for clinical applications requiring precision in following individual patients.

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* * *

Drs Genant and Cann Respond

To the Editor: Dr Powell has raised several important issues regarding our recent article.[1] Both quantitative computed tomography (QCT) and dual photon absorptiometry (DPA) represent important advances in the noninvasive measurement of bone mineral content in the spine. The former, QCT, provides a direct measure of trabecular bone density in grams per cu cm and the latter, DPA, provides an area projection measure of integral bone in grams per sq cm.

There are now over 100 centers in the United States that are either operational or in the process of becoming operational with QCT for vertebral mineral determination. The procedure can be readily applied to most of the 2,000 advanced computed tomographic (CT) scanners currently functioning in the United States and at a relatively small cost of $500 for procurement of a calibration phantom along with protocols for scanning and data analysis.[2,3] For quantitative studies, the CT scanner is generally operated at one-tenth the standard radiation exposure[4] used for diagnostic CT imaging and the procedure requires approximately 10 to 15 minutes of patient time so that three to four studies can be performed in one hour at an economical rate. For most scanners, data analysis can be fully automated and performed by the technologist in five to ten minutes.

There are approximately 25 centers in the United States currently becoming operational for DPA, which requires an initial investment of $30,000 to $60,000 for equipment that is limited solely to bone mineral analysis and requires dedicated space and special technological training. Scanning time for DPA is approximately 30 to 40 minutes. While the radiation exposure required for dual photon absorptiometry is less than that for quantitative CT, the use of an accompanying conventional radiograph of the spine to identify vertebral levels, fractures, osteophytes, etc. raises the total radiation exposure of this technique to a level comparable to that of quantitative CT. Nevertheless, the radiation exposure required for both techniques is in an acceptable range for serial diagnostic studies.

The precision (reproducibility) of quantitative CT is 1.5% to 3%, which is approximately the same as dual photon absorptiometry, while the sensitivity for mineral change is perhaps two-fold greater since QCT measures purely trabecular bone rather than an integral of trabecular and compact bone as with DPA.[1,3] The accuracy for vertebral specimens, in vitro, for both QCT and DPA is approximately 5% to 10% for most applications but may be poorer in the elderly populations for both techniques but for differing reasons.[5] In the case of DPA, vertebral compressions, hypertrophy of articular facets, discogenic sclerosis or marginal osteophytosis and extra-osseous calcification, which are widespread in the elderly and are included in the integral measurement, may result in inaccurate as well as poorly reproducible vertebral measurements.[7] In the case of QCT, the sources of error are different but are partially correctable. The density of yellow marrow is

less than that of red marrow because of the presence of fat, which falsely reduces the measured spinal mineral value. The use of dual energy QCT using preprocessing or postprocessing techniques can reduce this fat-induced error in the elderly to 2% to 4%, but it is considered unnecessary for most clinical applications because the inaccuracy is small relative to the normal biological range.[5,8] Furthermore, the inaccuracies in the elderly population for both QCT and DPA should be placed in perspective by recognizing that even the widely cited quantitative histomorphometry has a sampling error of approximately 20% for determining trabecular bone volume.

In summary, quantitative computed tomography of the vertebral spongiosum is a rapid, sensitive, precise and acceptably accurate method for noninvasive measurement of bone mineral mass. The potential advantage of QCT over dual photon absorptiometry is its capability for exact three-dimensional anatomic localization providing a highly precise and highly sensitive measurement of vertebral trabecular bone. Furthermore, it has the potential advantage of very widespread distribution and nearly universal availability.

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Does *El Niño* Also Cause Diarrhea?

To the Editor: *El Niño,* the warm current off the coast of California, has received much publicity. Many alterations in weather and in the fishing industry have been attributed to *El Niño.* We have recently isolated *Vibrio parahemolyticus* from a patient who ingested raw local oysters and developed gastroenteritis. This organism is commonly found in the warm waters of the Gulf of Mexico during the summer months and is an atypical cause of gastroenteritis in the usual cold waters of northern California. It is possible that with *El Niño* more clinical cases of *Vibrio parahemolyticus* gastroenteritis will be seen in California.

Vibrio parahemolyticus is a halophilic Gram negative rod associated with acute gastroenteritis resulting from eating either raw or improperly prepared shellfish. It is a major cause of diarrhea in Japan where raw seafood is commonly ingested.[1] *Vibrio parahemolyticus* causes clinical disease in the warmer months when the organism is found within the zooplankton.[2] During this period the organism incidentally infects shellfish. The *Vibrio parahemolyticus* generally is confined to the mud in the colder months and rarely causes clinical disease.

Explosive diarrhea and abdominal cramping are the major clinical features and fewer than 50% of patients will have fever or vomiting. The incubation period ranges from 5 to 96 hours with an average time of 24 hours. The gastroenteritis is generally self-limited and requires no treatment other than supportive therapy.

Vibrio parahemolyticus is best cultured on TCBS media (thiosulfate-citrate-bile salt-sucrose) which is not commonly utilized for routine diarrhea specimens. The self-limited nature of the disease and improper culturing methods make a culture confirmation difficult. This could explain the current paucity of cases of *Vibrio parahemolyticus* in California.

The present warmer ocean temperatures due to *El Niño* favor clinical disease by *Vibrio parahemolyticus.* When gastroenteritis results following ingestion of seafood the proper culture media should be utilized in attempting to isolate *Vibrio parahemolyticus.*

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Physician Involvement in Community Activities

To the Editor: I read with interest the editorial in the October 1983 issue regarding physicians on school boards.[1]

I do not know what was the genesis of the editorial but as a nine-year veteran of the Carlsbad (California) Unified School District Board of Trustees I can surely support the opinions you expressed. Among the many perils that have beset medicine, some of the most serious are of our own making. The refusal of physicians to become involved in their communities politically and educationally are two of the most damaging. Whether your editorial will awaken an interest in your readers regarding this type of service is problematic because from my vantage point I see no evidence that my peers are altering this very self-destructive course.

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Diagnosis and Treatment of Prostatitis

To the Editor: Articles that review prostatitis for nonurologists never seem to give clinicians an idea of the relative frequency of the various types. Hence, I make a few comments to supplement Dr Shortliffe's presentation in the October issue.[1]

Acute bacterial prostatitis is a very *un*common disease. I have been impressed that the patients may simply have a flu-like syndrome of headache, myalgia and fever for 24 to 48 hours *before* any urinary tract symptoms ever develop. Having a high index of suspicion and doing an analysis of urine will yield the diagnosis. Chronic bacterial prostatitis is likewise an uncommon entity, and the treatment is as Dr Shortliffe outlined.

Abacterial prostatitis is by far the most common entity. It seems to be precipitated in many instances by stress in the broadest sense of the term (fatigue, another illness or traveling, for example). Why this inflammatory problem seems to respond so well to trimethoprim-sulfamethoxazole I am not sure. Perhaps the newer once-a-day anti-inflammatory drugs (such as Indocin SR) would be a better way to initiate therapy. Crucial to the patient's getting better is an explanation that this is a benign problem, albeit a nuisance, and that it may come and go. Caffeine (a prostatic irritant) may exacerbate symptoms and sitz baths will alleviate mild to moderate discomfort.

Prostatodynia is a poor term. Either the patient has prostatitis (even if massage did not happen to express pus from the involved portion of the gland) or he does not—and another term should be used. Regardless, inflammation *is* present or the patient would not have symptoms, and I concur with Dr Shortliffe that anti-inflammatory drugs, muscle relaxants and sitz baths may all be useful.

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Community Hospital CME—Its Proper Place

To the Editor: In the September 23 edition of *JAMA* is the annual summary of medical education in the United States, 1982-1983. But again, as has been the case previously, the space and interest devoted to community-hospital-based continuing medical education (CME) is piteously brief, especially when compared with the attention lavished on other aspects of medical education and training. Moreover, when one considers the magnitude of desired and required continuing postgraduate training as reflected in the extensive time and effort devoted to credentialing new medical staff applicants, proctoring them subsequently and then recredentialing them periodically for maintenance of medical-surgical skills, the problems of hospital-based CME activities come into even sharper focus.

Additionally, if anybody is interested in it (and we really are or ought to be), the expense of university-sponsored CME programs to attending private practitioners is very considerable indeed. For an average internist, the cost merely begins with a $350 fee for a typical two-day conference. Add to that the cost of travel and lodging plus loss of income, one is conservatively looking at expenses of $1,600 to $1,900, some of which might well be replaced by sophisticated community-hospital-centered CME activities.

The treatment of this kind of postgraduate study, although substantially better than four to five years ago, is symptomatic of our relative neglect of community hospital CME. The attention and assistance dedicated to it at higher organizational levels of state medical associations and the American Medical Association are insufficient. Some serious effort on the part of organized medicine is due now, without the delay of another year, for the purpose of enhancing the quality and availability of community-hospital CME activities.

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Topics in Primary Care Medicine

Chemoprophylaxis Against Tuberculosis

DIANA LEWIS COLEMAN, MD, *and* GARY SLUTKIN, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Mycobacterium tuberculosis can persist in a dormant state in asymptomatic infected people for years. These infected persons remain at risk throughout their lives for subsequent reactivation of the tubercle bacillus and, therefore, for the development of tuberculous disease. Chemoprophylaxis with isoniazid can prevent future tuberculous disease from developing in infected persons.

Benefits of Isoniazid Chemoprophylaxis

Isoniazid has been tested in more than a dozen prospective, randomized, placebo-controlled trials involving more than 100,000 people. These trials have been conducted for several populations including household contacts, tuberculin skin test converters, infected persons with stable radiographic lesions and negative bacteriologic examinations and child and adolescent skin-test reactors. Twelve months of taking isoniazid daily confers 70% to 90% protection against future tuberculosis; six months of therapy provides 50% to 60% protection. This protection has lasted 20 years and is likely to last a lifetime.

Preventive therapy with isoniazid is practical because both screening for the infected state and treatment with isoniazid are efficacious, inexpensive and safe. Screening for tuberculous infection is done by the tuberculin skin test.

The Tuberculin Skin Test

The tuberculin skin test is the most sensitive and specific means available for diagnosing infection due to *M tuberculosis* in the absence of culture-documented disease. Skin testing with purified protein derivative (PPD) using 0.1 ml of the 5 TU strength, administered by the Mantoux (intradermal) method, is the only standard technique recommended. Multiple-puncture techniques such as Tine testing are less reliable. The skin test should be read at 48 to 72 hours and recorded as millimeters of induration (not erythema) and not simply as "positive" or "negative."

No clear point of separation between significant and nonsignificant skin test reaction sizes can be defined to cover all clinical and epidemiologic circumstances. In most circumstances in the United States, a reaction size of 10 mm or more of induration is accepted as being specific and sensitive enough for an accurate diagnosis of tuberculous infection. The larger the reaction size, the greater the certainty that the reaction is due to sensitization from *M tuberculosis*.

The ability of a given size of tuberculin reaction—such as 10 mm—to predict infections with *M tuberculosis* is also increased when (1) the prevalence of exposure to cross-reacting mycobacteria is low, such as in Alaska where nontuberculous (atypical) mycobacteria are uncommon; and (2) in situations where the prevalence of *M tuberculosis* infection is high—for instance, when there are close contacts with patients who have active pulmonary tuberculosis. In these circumstances, reaction sizes of less than 10 mm of induration may have the same predictive value that 10 mm of induration has for the general population in the United States. Specifically, for persons who are close contacts of patients who have active pulmonary

(Coleman DL, Slutkin G: Chemoprophylaxis against tuberculosis [Topics in Primary Care Medicine]. West J Med 1984 Jan; 140:106-110.)

From the Pulmonary Division, Department of Medicine, University of California, San Francisco; The Chest Service, Department of Medicine, San Francisco General Hospital Medical Center, and The Division of Tuberculosis Control, Department of Public Health, San Francisco.

Reprint requests to Gary Slutkin, MD, Clinical Director, Division of Tuberculosis Control, Ward 94, SFGH Medical Center, 1001 Potrero Avenue, San Francisco, CA 94110.

TABLE 1.—*Risk of Future Tuberculous Disease Among Tuberculin Reactors*

Group I	
No Additional Risk Factors	
Reactive PPD* of unknown duration, patient older than 5 years of age, normal chest film	0.1% per year
Group II	
Newly Infected	
Recent skin test converter	3%-5% in first year
Household contact	
Positive skin test initially	5.0% in first year
Overall	2.5% in first year
Group III	
Large Residual Bacillary Load	
Reactive PPD, abnormal chest film, inadequate past therapy	1%-4.5%† per year
Group IV	
Special Medical Circumstances‡	
Silicosis, insulin-dependent diabetes mellitus, hematologic or reticuloendothelial malignancy, gastrectomy, ileal bypass, dialysis for chronic renal failure, prolonged glucocorticoid or immunosuppressive therapy	

*PPD = tuberculin skin test with purified protein derivative.
†Higher if prior activity within last five years or if no prior therapy.
‡Risk increased but generally accepted estimates not available.

tuberculosis, skin test readings of 5 mm or more of induration should be interpreted as significant.

Tuberculin reactivity following bacille Calmette-Guérin (BCG) vaccination varies greatly. Because there is no reliable way to differentiate a reaction due to prior BCG vaccination from that due to natural infection with *M tuberculosis,* it is prudent in most situations to ignore a history of BCG vaccination when interpreting a tuberculin skin test reading.

Interpretation of tuberculin skin test conversions is frequently confusing. Skin test conversion is defined as an increase in the size of a reaction by 6 mm or more from less than 10 mm to more than 10 mm within two years. The importance of a skin test conversion is that it allows identification of newly infected persons. Not all apparent conversions represent recent infection, however. First, falsely depressed reactions (even to no induration) occur for many reasons, including poor skin test administration or reading technique, patient immunosuppression or coexisting diseases such as viral infections. If the factor(s) responsible for the falsely depressed reaction are corrected or reversed, and a repeat test is found to be reactive, persons may be mistakenly considered newly infected.

Second, tuberculin reactivity may wane in older persons because of the long interval between their initial infection and their subsequent skin test. In this situation, greater reactivity may be seen on a repeat test because of the "resensitization" that results from the first test. This greater reactivity is called the booster effect and does not represent a new tuberculous infection. When annual skin testing is anticipated (such as in hospital employees), two-step testing at the initial evaluation is recommended. Nonreactors are retested one to two weeks after the first skin test. Those that react on the second test have exhibited a booster effect and should be classified as skin test reactors but not as skin test converters.

In general, those skin test converters who are young (that is, younger than 20 years of age) or who are household contacts of patients with active pulmonary tuberculosis, should be considered newly infected.

Risks of Future Tuberculous Disease

The risk for development of tuberculous disease can be approximated for four groups of infected persons (Table 1). First, tuberculin reactors of unknown duration without additional risk factors have an annual rate of subsequent tuberculous disease occurring of approximately 0.1% per year. This small annual risk becomes significant when expected lifetime cumulative risk is considered. For example, a 20-year-old reactor expected to live an additional 55 years has a calculated lifetime disease risk of 5.5%.

Second, newly infected patients including recent skin test converters and household contacts of patients with active pulmonary tuberculosis have a much greater risk of tuberculous disease developing during the first year after becoming infected (2.5% to 5%) than reactors of unknown duration have per year.

Third, infected persons who harbor large residual numbers of tubercle bacilli have a greater yearly risk of tuberculous disease developing (1.0% to 4.5%) than reactors of unknown duration (Table 1). This group includes infected patients with both reactive skin tests and chest film changes consistent with prior tuberculosis. The presence of calcified granulomas or localized pleural changes on the chest film does not, however, indicate significantly increased risk. Fourth, reactors who have special medical circumstances, as listed in Table 1, are frequently cited as being at increased risk for subsequent tuberculous disease, though generally accepted risk estimates are not available.

Risks of Isoniazid Prophylaxis

Serious adverse reactions to isoniazid given for chemoprophylaxis are uncommon. Mild central nervous system intolerance including minor difficulties with concentration and feelings of dizziness or minor depression or euphoria are the most frequent type of adverse re-

TABLE 2.—*Groups of Persons With Reactive Tuberculin Skin Tests for Whom Isoniazid Preventive Therapy Is Recommended*

- Group I
  - Preventable lifetime risk of tuberculosis >risk of isoniazid toxicity
    - <5 years old—mandatory
    - 5-20 years old—highly recommended
    - 21-35 years old—controversial
- Group II
  - Newly infected persons
    - Recent skin test converter (within 2 years)
    - Household contact
- Group III
  - Persons with presumed large residual bacillary load
    - Reactive PPD*, abnormal chest film, inadequate past therapy
    - Prior active disease, inadequate past therapy
- Group IV
  - Special circumstances
    - Patients with silicosis, insulin-dependent diabetes mellitus, hematologic or reticuloendothelial malignancy, prior gastrectomy or ileal bypass, renal failure requiring dialysis or prolonged use of glucocorticoid or immunosuppressive therapy
    - Infected persons whose reactivation may have severe public health consequences (for example, school teachers)

*PPD=tuberculin skin test with purified protein derivative.

action to isoniazid. Taking the drug at bedtime instead of in the morning usually alleviates these symptoms.

Although elevated levels of serum amino transferases may be found in 10% to 20% of persons receiving isoniazid chemoprophylaxis, clinical hepatitis that requires discontinuation of isoniazid is infrequent. Patient age is the major risk factor for the development of clinical hepatitis. It occurs in 0.3% of patients 20 to 34 years old, 1.2% of patients 35 to 49 years old and 2.3% of patients 50 to 64 years old. Alcohol use and the presence of chronic liver disease may enhance the risk slightly. Acetylation phenotype does not appear to modify risk estimates.

Isoniazid hepatitis presents as a nonspecific gastrointestinal or flulike illness. Symptoms are most common in the first four to eight weeks of therapy but may occur any time. Only 10% of patients present with jaundice. Fever, rash and splenomegaly are uncommon. Up to 20% of patients have a leukocytosis; eosinophilia is rare. Serum aspartate and alanine amino transferase values are both elevated; however, there is no consistent relationship between the levels of these two amino transferases. When isoniazid is promptly discontinued, isoniazid hepatitis resolves (usually within days) without sequelae. Death can result from continued drug administration, but this is extremely rare now because of improved physician awareness and patient education about this problem.

Patients should be instructed to seek medical attention if they have more than two to three days of anorexia, malaise, nausea, vomiting or other nonspecific symptoms. If symptoms are severe, a patient should discontinue isoniazid therapy. Serum amino transferase levels should be measured. Even if symptoms are mild, if the aspartate amino transferase value is increased, isoniazid should be discontinued. Other causes of hepatitis such as viral should also be sought. Usually a patient's symptoms are mild and transient, not due to isoniazid and amino transferase values are found to be normal.

Most experts do not recommend routine determination of serum amino transferase levels before starting or during isoniazid chemoprophylaxis. For persons with habitual alcohol consumption or suspected chronic liver disease, however, one pretreatment aspartate amino transferase value may help to prevent confusion if symptoms arise later.

A pyridoxine-responsive peripheral neuropathy is seen in less than 1% of persons receiving isoniazid. Pyridoxine hydrochloride therapy (5 to 10 mg daily) is recommended for pregnant women, for elderly patients and for patients who are severely malnourished, a predisposition for peripheral neuropathy to develop (such as persons with diabetes, alcoholism or uremia) or seizure disorders.

Isoniazid interacts with both phenytoin (Dilantin) and disulfiram (Antabuse). Isoniazid interference with the metabolism of phenytoin may result in phenytoin toxicity. Therefore, five to ten days after initiating isoniazid preventive therapy, a patient should be reevaluated and the phenytoin concentration should be measured. The dosage of phenytoin will frequently need to be decreased; the dosage of isoniazid should not be changed. The combination of isoniazid and disulfiram may cause behavioral changes as a result of their additive effects on dopamine metabolism. Introducing the new drug at gradually increasing doses may help allow early detection of such behavioral changes.

Rarely, isoniazid can cause fever, skin rashes or a lupus erythematosus-like syndrome.

Recommendations for Therapy

Isoniazed chemoprophylaxis for tuberculosis is recommended for infected persons who have a high risk of subsequent tuberculous disease when the expected benefit of isoniazid therapy (a reduction of 70% to 90% of total future risk) is greater than the risk of a significant adverse reaction to isoniazid (primarily hepatitis). When considering cumulative lifetime risks for tuberculosis, most experts agree that the risk of preventable tuberculosis is far greater than that of hepatitis for reactors younger than 21 years of age (Table 2). Thus, isoniazid chemoprophylaxis is recommended for all persons younger than 21 years even in the absence of additional risk factors. Chemoprophylaxis is considered mandatory for reactors younger than 5 years old because tuberculous infection in these young patients progresses more often to life-threatening illness (progressive pulmonary, miliary and meningeal disease) than in older children.

Controversy surrounds the recommendations for isoniazid prophylaxis for the 21- to 35-year-old reactor with no additional risk factors. For this group, the risk of preventable tuberculous disease is greater than the risk of isoniazid-hepatitis. However, both risks are

TABLE 3.—*Before Beginning Isoniazid Preventive Therapy*

Exclude active pulmonary tuberculosis
Chest film
If chest film abnormal, sputum smears and cultures for *Mycobacterium tuberculosis*
Identify contraindications to therapy
Prior adequate therapy
Prior adverse reaction to isoniazid
Acute liver disease
Identify possible complicating situations
Habitual alcohol abuse
Chronic liver disease
Pregnancy
Other drugs—phenytoin, disulfiram

small. Tuberculosis is treatable and isoniazid-hepatitis is reversible in a patient who discontinues taking isoniazid promptly if symptoms occur. Tuberculosis has consequences that may involve the health of family members and other close contacts. However, effective isoniazid prophylaxis requires a year of daily pill taking by the reactor. Patients differ greatly in their own assessment of the consequences of these competing risks. We prefer to actively involve reactors in this age range in the isoniazid therapeutic decision.

The additional risk factors listed in Table 1 increase a reactor's chance of tuberculosis developing so much so that isoniazid preventive therapy is justified for them at almost any age. Isoniazid preventive therapy is therefore recommended for recent (within two years) skin test converters and household contacts of patients with active pulmonary tuberculosis (newly infected persons), for tuberculin reactors with inadequate (or no) prior therapy who have an abnormal chest film examination compatible with prior active tuberculosis (persons who presumably harbor large residual numbers of tubercle bacilli) and for persons with special medical circumstances (Table 2). Isoniazid preventive therapy should also be considered on an individual basis for skin test reactors older than 21 years of age when, because of special circumstances of employment, tuberculous disease developing in them may have severe public health consequences, such as in the case of nursery school teachers.

Because household contacts of patients with active pulmonary tuberculosis are at such increased risk for tuberculosis developing, isoniazid prophylaxis should be initiated even for those contacts whose initial skin test is nonreactive (less than 5 mm in this circumstance), if the index case is smear positive, the contact's exposure was intense or if the contact is very young (younger than 5 to 10 years of age). Contacts with nonreactive skin tests should be retested in two to three months. If the skin test remains nonreactive, a contact's isoniazid regimen can be discontinued if the index case has been receiving chemotherapy or if the index case no longer has household contact with the nonreactor. If a contact's repeat skin test becomes 5 mm or more, isoniazid therapy should be continued for a year.

Recommendations for isoniazid preventive therapy during pregnancy are controversial. Isoniazid appears to be safe in pregnancy. No excess fetal loss, premature births, low-birth-weight infants or congenital malformations have been seen in more than 1,400 pregnancies during which isoniazid was used. However, because preventive therapy is elective, we recommend deferring administering the drug until after delivery for reactors of unknown duration without additional risk factors. For higher risk patients (for instance, those with household contact, recent skin test converters or those with abnormal findings on chest film), we believe isoniazid preventive therapy should be given without delay. In these situations the primary goal is to prevent active disease from developing in a mother and *M tuberculosis* being transmitted to her infant. Undetected disease in an infant can be catastrophic.

Initiating Isoniazid Preventive Therapy

Before beginning isoniazid preventive therapy, active tuberculosis must be excluded and contraindications to therapy or possible complicating medical situations must be identified (Table 3). A chest film should be taken on all skin test reactors. If the findings are abnormal and consistent with tuberculous disease, prior chest films should be reviewed and three sputum specimens should be stained and cultured for tuberculosis. In this situation, it is usually advisable to begin therapy with two or more antituberculous medications for possible active disease if chest film abnormalities are extensive, if a reactor is symptomatic or if small children are in the home. If bacteriologic evaluation is negative and no clinical or radiologic response occurs after two to three months, active tuberculosis is unlikely and therapy can be reduced to isoniazid only for prophylaxis.

Taking a detailed history will identify patients with contraindications to isoniazid preventive therapy and with possible complicating medical problems. In most circumstances, patients should not receive isoniazid preventive therapy if they have already received adequate therapy for active disease or for prophylaxis, if they have had previous adverse reactions to isoniazid or if they have acute liver disease of any cause. Patients who use alcohol habitually or who have chronic liver disease should be identified and a pretreatment serum aspartate amino transferase determination should be done. Women should be questioned about possible pregnancy and all patients should be thoroughly questioned about the use of other medications.

For preventive therapy in adults, isoniazid is given once a day as a single 300-mg tablet for one year. Children should be given 5 to 10 mg per kg of body weight a day to a maximum of 300 mg, for one year. Suspensions of isoniazid in sorbitol can be prepared for children who cannot take tablets. Patients should be educated about the symptoms of isoniazid hepatitis at their initial visit and they should be reminded during return visits. A symptom checklist may be useful for physicians or clinics that commonly prescribe isoniazid. Return visits should be scheduled every one to three months depending on a staff's perception of a patient's ability to recognize and report symptoms suggestive of

an adverse reaction to isoniazid. At the end of 12 months of isoniazid therapy, patients can be discharged without the need for additional follow-up. Routine radiographic studies at the completion of therapy are not necessary.

Chemoprophylaxis for Suspected Isoniazid-Resistant Infection

Preventive treatment of suspected isoniazid-resistant *M tuberculosis* infection is a controversial problem. Isoniazid resistance is found in 8% to 20% of sputum isolates in patients from Mexico, Central America and Asia with pulmonary tuberculosis. Although some experts believe isoniazid could still be useful to prevent tuberculous disease in persons infected with resistant organisms, many failures have been reported. No drug other than isoniazid has yet been tested for chemoprophylaxis although most experts believe rifampin will prove effective. For most foreign-born reactors who are candidates for chemoprophylaxis, isoniazid is still recommended. For young children who are close contacts of patients with pulmonary tuberculosis due to known isoniazid-resistant organisms, it may be safest to treat with rifampin (with or without isoniazid).

Screening for Tuberculosis in an Ambulatory Setting

Because of the relatively low prevalence of tuberculosis in the United States, most departments of public health no longer screen or recommend screening for tuberculosis in the general outpatient population. Instead, screening efforts are concentrated in groups with a higher prevalence of disease such as immigrants and close contacts of people with active pulmonary tuberculosis.

For most healthy outpatients, skin testing should be done if a reactive test would change the management of the patient. Therefore, for children younger than 5 years of age, annual skin testing is recommended. The finding of a reactor younger than 5 years of age should prompt further investigation to find the source of the infection. For persons aged 5 to 20 years old, tuberculin skin tests should be done every one to four years. For most persons older than 20 years of age, periodic skin testing is not necessary.

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Health Care Delivery

EDITOR'S NOTE—*The issues involving "no code" or "do not resuscitate" (DNR) orders are many and complex. They are often of particular concern to younger physicians serving as house officers but are of importance to any physician caring for a patient whose outlook is considered to be poor or hopeless. The three articles presented in this mini-symposium describe the problem as addressed in three different environments.*

Do-Not-Resuscitate Orders in a County Hospital

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The use of the do-not-resuscitate order has become accepted medical practice. To date, however, no study has been done of how often it is used or factors associated with its use. Reports of all deaths of inpatients occurring during calendar year 1981 at San Bernardino County Medical Center were eligible for study. Retrospective review of the 237 cases indicated that a do-not-resuscitate order had been written for 165 (69.6%) of the patients. Comparison of reports of those for whom such an order had been written with those for whom no order had been written indicated that a do-not-resuscitate order was not associated with age, sex, ethnicity or pay status. Indices of mental clarity, however, were associated with orders not to resuscitate; those patients residing in nursing homes, and not alert and oriented on admission were overrepresented in the group given this order. Primary discharge diagnosis was also associated with such an order, as was an increased duration of hospital stay.

(Levy MR, Lambe ME, Shear CL: Do-not-resuscitate orders in a county hospital [Health Care Delivery]. West J Med 1984 Jan; 140:111-113.)

THE WRITING of a do-not-resuscitate order (defined as a doctor's order to withhold cardiopulmonary resuscitative efforts in the event of acute cardiac or respiratory arrest) has become an accepted practice in the care of terminally ill patients.[1] General ethical guidelines and considerations for the use of a do-not-resuscitate order continue to be published in the medical literature.[1-4] To date, however, no study has been done that describes the magnitude of this practice, the patient factors that are associated with its use, its effect on the quality of a patient's remaining life or its effect on the use of costly inpatient health care services. Such information would assist medical professionals to use the do-not-resuscitate order in an ethical and cost-effective manner.[5] We describe a first attempt to estimate the above-mentioned factors.

Patients and Methods

The cases of all patients who died during their hospital stay at the San Bernardino County Medical Center during the 1981 calendar year were identified retrospectively. The San Bernardino County Medical Center Hospital is a teaching hospital of medium size (about 300 beds). Decisions not to resuscitate are not controlled by a formal clinical care committee, but rather by the house staff and attending physicians directly involved in a patient's care.

Demographic information on patients was obtained from medical records. The information collected included age, sex, ethnicity and pay status—that is, whether a patient was covered by MediCal, Medicare, a third-party insurer or was personally responsible for medical costs.

Two indices of a patient's mental clarity on admission were used. These crude measures were place of residence before admission (private residence, nursing home or other) and mental state on admission (alert and oriented to time, place and person, or other) from the admission history and physical. In addition to these indices of function, the association between a do-not-resuscitate order given during a prior admission and its use in the terminal admission was assessed.

Measures of the course of hospital stay included admitting service, number of days in hospital and primary cause of death. This latter information was obtained from autopsy reports when available or from discharge summaries. Diagnoses were coded into the 17 major categories of the *International Classification of Diseases* (9th revision), *Clinical Modification.*

Additional information was collected to describe the

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effect of a do-not-resuscitate order on a physician's care of a patient and how family and friends interacted with the patient. Considerations included narcotic use (defined as the percentage of the number of days in hospital for which any narcotic was given) and visit days (defined as the percentage of days in hospital the patient had a visitor as noted in the nursing notes).

To determine the association between the use of do-not-resuscitate order and the above-mentioned factors, deaths were divided into two groups; those that occurred after such an order was issued and those for which no do-not-resuscitate order was issued. An association was tested using standard χ^2 and Student's t tests.

TABLE 1.—*Association Between Selected Demographic Variables and a Do-Not-Resuscitate Order in 237 Patients*

Demographic Characteristics	Do-Not-Resuscitate Order: Yes N (%)	Do-Not-Resuscitate Order: No N (%)
Age (years)		
0- 9	14 (8.4)	6 (8.3)
10-29	15 (9.1)	8 (11.1)
30-49	12 (7.3)	13 (18.1)
50-69	50 (30.3)	17 (23.6)
70+	74 (44.8)	28 (38.9)
TOTAL	165 (100.0)	72 (100.0)
Sex		
Male	98 (59.4)	42 (58.3)
Female	67 (40.6)	30 (41.7)
TOTAL	165 (100.0)	72 (100.0)
Ethnicity*		
White	118 (72.0)	43 (59.7)
Hispanic	30 (18.3)	15 (20.8)
Other	16 (9.7)	14 (19.5)
TOTAL	164 (100.0)	72 (100.0)
Pay Status*		
Medicare	92 (57.9)	30 (46.1)
MediCal	11 (6.9)	10 (15.4)
Self-pay	45 (28.3)	20 (30.8)
Private—3rd party	11 (6.9)	5 (7.7)
TOTAL	159 (100.0)	65 (100.0)

*Ethnicity and pay status totals reflect missing data for 1 and 13 patients, respectively.

TABLE 2.—*Association Between Place of Residence, Level of Consciousness on Admission and a Do-Not-Resuscitate Order*

Characteristics	Do-Not-Resuscitate Order: Yes N (%)	Do-Not-Resuscitate Order: No N (%)
Place of Residence*		
Home/family	89 (53.9)	55 (78.6)†
Nursing home	60 (36.4)	8 (11.4)†
Other	16 (9.7)	7 (10.0)†
TOTAL	165 (100.0)	70 (100.0)†
Consciousness on Admission*		
Alert and oriented to time, place and person	45 (27.4)	28 (38.9)
Other	119 (72.6)	44 (61.1)
TOTAL	164 (100.0)	72 (100.0)

*Place of residence and consciousness on admission reflect missing data for 2 and 1 patients, respectively.
†$P<.01$.

Results

During calendar year 1981, 315 patient deaths were recorded. Fifteen stillbirths were excluded from the analysis. Of the remaining 300 patients, complete charts were available for 237 (79%). Only these cases are included in the analysis.

Of the 237 eligible cases, 165 (69.6%) had a do-not-resuscitate order written during their hospital stay. Of the 165 cases, 81 (49.1%) had this order written during the first two days of their hospital stay. On the average, five hospital days elapsed between the time a do-not-resuscitate order was written and the time a patient died.

Demographic characteristics of the total sample were as follows. More than 70% of the patients were 50 years of age or older, 59% were male, 68% were white and 19% were Hispanic. Only 7% were covered by private, third-party health insurance. Comparing demographic characteristics of patients for whom a do-not-resuscitate order was written with those for whom no such order was written showed no statistically significant associations with age, sex, ethnicity or pay status (Table 1).

Comparison of the crude indices of mental clarity on admission of the do-not-resuscitate order group indicated that less functional patients were more likely to have a do-not-resuscitate order. Place of residence was associated with the decision not to resuscitate ($P<.01$), with 88.2% of patients from nursing homes being in that group. Those who were not alert and oriented to time, place and person also tended to be overrepresented in the do-not-resuscitate group; however, statistical significance was not reached (Table 2).

No admitting service tended to have more do-not-resuscitate orders than any other. A striking finding was that 100% of those patients with a no-code order on prior admission had such an order on the terminal admission, whereas 70% of those without a prior do-not-resuscitate order had such an order on the terminal admission ($P<.05$) (Table 3).

Primary discharge diagnosis was positively associated with a written do-not-resuscitate order ($P<.01$). Categories of diagnosis overrepresented in that group included nonspecific signs and symptoms (primarily septic shock), respiratory conditions (primarily pneumonia), intra-abdominal conditions (primarily renal failure), infectious diseases (primarily septicemia), neonatal distress (primarily due to extreme immaturity) and neoplasms (Table 4).

The mean duration of hospital stay for those patients with a do-not-resuscitate order was 14.2 days

(Table 5). For patients who had no such order written, the mean duration was 7.9 days. This trend was statistically significant. Neither the number of visits by friends and family nor narcotic use was associated with the presence of a no-code order. Moreover, these aspects of a patient's care did not change after a do-not-resuscitate order was written (Table 5).

TABLE 3.—*The Association Between Order Not to Resuscitate on Prior Admission, Current Admitting Service and a Do-Not-Resuscitate Order in 237 Patients*

Characteristics	Do-Not-Resuscitate Order: Yes N (%)	Do-Not-Resuscitate Order: No N (%)
Do-Not-Resuscitate Order Given in Prior Admission*		
Yes	13 (8.3)	0 (0.0)†
No	143 (91.7)	62 (100.0)†
TOTAL	156 (100.0)	62 (100.0)†
Current Admitting Service		
Medicine	115 (69.6)	48 (66.7)
General surgery	15 (9.1)	9 (12.5)
Neurosurgery	10 (6.1)	6 (8.3)
Neonate intensive care unit	12 (7.3)	6 (8.3)
Other	13 (7.9)	3 (4.2)
TOTAL	165 (100.0)	72 (100.0)

*No prior admission for 19 patients.
†$P<.05$.

TABLE 4.—*Association Between Primary Discharge Diagnosis and a Do-Not-Resuscitate Order in 237 Patients*

Primary Discharge Diagnosis Category*	Do-Not-Resuscitate Order: Yes N (%)	Do-Not-Resuscitate Order: No N (%)
Nonspecific signs and symptoms	12 (7.3)	1 (1.4)
Respiratory tract	38 (23.2)	8 (11.1)
Gastrointestinal tract	13 (7.9)	3 (4.2)
Genitourinary tract	12 (7.3)	3 (4.2)
Infectious disease	19 (11.6)	5 (6.9)
Neonatal distress	10 (6.1)	3 (4.2)
Neoplasm	8 (4.9)	3 (4.2)
All other	12 (6.7)	6 (8.2)
Cardiovascular	29 (17.7)	25 (34.7)
Injury/poisoning	10 (6.1)	12 (16.7)
Metabolic/endocrine	2 (1.2)	3 (4.2)
TOTAL	165 (100.0)	72 (100.0)

*$P<0.01$.

TABLE 5.—*Association Between Narcotic Use, Visits By Outsiders, Duration of Hospital Stay and a Do-Not-Resuscitate Order*

Characteristics	Do-Not-Resuscitate Order: Yes, Before Order	Do-Not-Resuscitate Order: Yes, After Order	Do-Not-Resuscitate Order: No
Mean duration of hospital stay (days)*	9.0	5.2	7.9
Narcotic use (%)†	14.5	13.9	13.8
Visits by outside persons‡	20.8	20.0	17.8

*$P<.05$ no do-not-resuscitate order.
†Percentage of mean days narcotic drug given to mean days in hospital.
‡Percentage of mean days in which a visit occurred to mean days in hospital.

Discussion

Assuming that a formal decision not to resuscitate indicates a patient is hopelessly ill, the high prevalence of such orders in this study indicates that most deaths that occur in this type of institution are not unexpected. This study includes only deaths, so that the extrapolation of this figure to all admissions is unwarranted. In addition, as the data source was medical charts, their validity is questionable. This is especially true for information on narcotic use and frequency of visitors. However, as the error in information is likely to be equal for the two groups of patients (do-not-resuscitate order versus no such order), the direction of bias would be toward no association.

These results indicate that demographic characteristics of patients play a minor role in the decision to write a no-code order. While no apparent trend of sex, ethnicity or pay status was present, those in the 10- to 39-year-old age bracket were less likely to have such an order written. The results indicate that the do-not-resuscitate orders are being written in good faith, without regard to sex, race or socioeconomic status. The trend by age is most likely a result of the severity of illness.

It appears that the ability of a patient to function and a patient's prognosis play the greatest roles in the decision to give a do-not-resuscitate order. This is evidenced by the greater number of orders written for nursing home residents, those who are not alert and oriented on admission and those whose diagnosis carries a poor prognosis.

The lack of change in number of visits received by a patient or of administration of narcotics when a do-not-resuscitate order was written does not indicate the order's lack of effect on a physician or a patient's family. These measures were crude indicators and of questionable validity.

The duration of hospital stay was greater for those patients for whom a do-not-resuscitate order was written. While the natural history of disease experienced in the two groups may account for the difference in duration of stay, these results do not support the theory that no-code orders help avoid an unnecessary use of expensive inpatient services. On the average, patients with a do-not-resuscitate order survived for about five days following the order's initiation.

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Epidemiology of No-Code Orders in an Academic Hospital

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Relatively little is known about the circumstances in which decisions not to resuscitate, documented by no-code orders, are made. By review of medical records and interviews with house staff officers, we studied all medical service patients for whom no-code orders were written and those patients who received cardiopulmonary resuscitation (CPR) between October and December 1980 in the Portland Veterans Administration Medical Center.

Among 1,780 patients admitted, 56 (3.1%) received no-code orders. All decisions were reportedly made by groups of individuals usually including the intern (98% of cases) and resident (93%), but not attending physician (39%). Many patients (43%) were disoriented or obtunded at the time of the no-code decision and 80% of oriented patients did participate in the decision.

Thirty-seven of the 56 no-code patients died during the study. Comparing these with 20 patients who experienced cardiac arrest and did receive CPR, cancer, dementia, incontinence, nonambulatory, divorced-separated and unemployed statuses were all more prevalent among no-code patients ($P<.05$).

No-code orders in this Veterans Administration teaching hospital were relatively common and appeared to be made collectively. Participation of patients and attending physicians in the decisions, however, was limited.

(Uhlmann RF, McDonald WJ, Inui TS: Epidemiology of no-code orders in an academic hospital [Health Care Delivery]. West J Med 1984 Jan; 140:114-116.)

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The opinions expressed herein are those of the authors and not necessarily those of the Robert Wood Johnson Foundation or the Veterans Administration.

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PHYSICIANS INCREASINGLY FACE what Cassem has termed their "most agonizing task"—judging when further medical intervention will not only fail but will also increase patient suffering.[1] With increasing frequency, it seems, physicians must weigh the appropriateness of administering cardiopulmonary resuscitation (CPR)[2] to certain patients. Because many cases are ambiguous,[3] it is enormously difficult to create all-encompassing legislation or even hospital policy to assist in these decisions. Policies governing "no-code" or "do-not-resuscitate" orders have nevertheless been formulated and promulgated by institutional or national expert groups.[4-7] Many authors have advocated specific moral or ethical approaches to assessing whether or not to withhold CPR. (See, for example, the review of Jonsen and colleagues.[8]) The applicability of these approaches is largely unknown because the factors influencing such decisions are not defined.

Empiric data concerning the de facto circumstances of decisions to withhold CPR would not tell us directly whether prevailing behavior is ethically sound; they would not even elucidate what principles are being invoked to make such decisions. Yet, by characterizing decisions actually being made in the existing climate of uncertainty, this information might suggest which principles can be applied and which are less feasible.

As a first step in acquiring such data we studied no-code decisions in one setting, a Veterans Administration teaching hospital, that lacked an operational no-code policy. We investigated the frequency of no-code orders and the involvement of various persons in these decisions. To develop hypotheses concerning what values are applied when making such decisions, we also identified characteristics of the study population for which the decision to withhold CPR was made.

Methods

This study took place at the Portland Veterans Administration Medical Center, a major teaching hospital of The Oregon Health Sciences University. At the time of this study neither the institution nor its Department of Medicine had a written policy regarding withholding resuscitation. The medical staff was required, however, to administer CPR to all patients who experienced cardiac arrest unless a written no-code order existed.

Two groups of patients were selected from among the 1,780 patients admitted to the inpatient medical service between October 1 and December 31, 1980. The first group, referred to as no-code patients, included 56 consecutive patients who received written no-code orders. These patients were identified by concurrently monitoring hospital patient charts and the hospital death log every one to two days.

The second group, referred to as CPR patients, included 20 consecutive patients who had cardiac arrest

and received cardiopulmonary resuscitation during the study period. These patients were identified by monitoring the mandatory reports filed on all CPR events.

Once a no-code patient was identified, the house officer who signed the order was interviewed. A questionnaire designed for the study requested information about the patient's mental state and ability to ambulate at the time of the decision not to resuscitate and the involvement and agreement of specific persons in the decision.

Four months after the close of the study, charts of no-code and CPR patients were reviewed to obtain the age, sex, race, employment, marital status, religion, place of residence, ability to ambulate, continence, diagnosis and survival of the patients. Diagnoses were examined as single entities and classified according to organ system or etiologic grouping as categorized in the *International Classification of Diseases*.[9]

Results

During the study period there were 56 no-code cases, constituting 3.1% of all medical service admissions, and 20 CPR cases. While the study was in progress, 34 no-code patients died and 3 died during the subsequent four months. None of the 20 CPR patients survived their hospital stay.

For all 56 no-code patients, an average of 4.4 (±1.2) persons was reportedly involved in the decision not to resuscitate. Most frequently involved were a resident, an intern, the patient (if oriented) and family (Table 1); 26 patients (46%), however, were disoriented or obtunded at the time the no-code decision was made. Eight patients (11%) had no known family. Four patients (7%) were both not oriented and had no known family. Of the participants included in the decision-making process (Table 1), those in the categories attending physician, nurse, consultant, medical student and clinic provider were reportedly involved in less than half of all cases. No social workers or chaplains were involved in any decisions. No opinions dissenting from the decision to withhold cardiopulmonary resuscitation were reported except for one instance, in which an intern disagreed with a no-code order that was later rescinded. When involved, the opinions of the patient, intern, family and clinic provider were considered most important (Table 1).

To determine if any patient characteristics were associated with a decision to withhold CPR, we compared the 37 nonsurviving no-code patients—that is, those who had cardiac arrest and did *not* receive CPR—with the 20 CPR patients—that is, those who had cardiac arrest and *did* receive CPR. Surviving no-code patients were excluded from this analysis in an attempt to make the no-code and CPR patients studied more nearly comparable with regard to severity of illness and prognosis. Of the 20 CPR patients, 17 were placed in an intensive care unit (ICU) before the cardiac arrest. The physicians of these patients clearly recognized their high-risk status prospectively and apparently intended these patients to receive CPR in the event of a cardiac arrest.

A comparison of nonsurviving no-code and CPR patients (Table 2) shows that a significantly greater proportion of the nonsurviving no-code patients were nonambulatory ($P<.01$), not working ($P<.05$), divorced or separated ($P<.05$) or incontinent ($P<.05$). Nonsurviving no-code patients were six years older

TABLE 1.—*Frequency of Participation and Importance of Participants' Opinions in Decisions Not to Resuscitate 56 Patients Admitted to Portland Veterans Administration Medical Center*

Participant	*Percent of Cases in Which Involvement Was Reported*	*Relative Importance of Involvement**†
Resident	98	2.2
Intern	93	2.8
Patient	43	2.9
Only if oriented (24 of 30)	80	
Family	61	2.6
Only if known to exist (34 of 48)	71	
Nurse(s)	45	1.6
Attending physician	39	2.1
Consultant(s)	25	1.9
Medical student	18	1.4
Clinic providers‡,§	17	2.6

*Scale: 0=not important; 1=minimally important; 2=moderately important; 3=very important.

†Means of importance scale ratings are indicated for cases in which involvement was reported.

‡Clinic providers included nine physicians and one nurse practitioner.

§Number of patients enrolled in clinics was unknown.

TABLE 2.—*Patient Characteristics*

	No-Code Nonsurvivors (N=37)		*CPR Nonsurvivors (N=20)*		
	Number Patients	*Percent Patients*	*Number Patients*	*Percent Patients*	*P Value*
Age	67.0±13.2* Years		61.0±11.7* Years		<.1
Employed	0	0	3	15	<.05
Marital Status					NS
Single	5	14	5	25	NS
Married	15	41	8	40	NS
Divorced/ separated	14	38	2	10	<.05
Widowed	2	5	2	10	NS
Other	1	3	3	15	NS
Continent	20/36†	56	12/13†	92	<.05
Ambulatory	8/36†	22	12/14†	86	<.01

CPR=cardiopulmonary resuscitation; NS=not significant.

*Standard deviations.

†The denominator is shown when patients of unknown status were excluded from the total.

TABLE 3.—*Independent Relationships of Patient Characteristics With Nonresuscitation Status*

	*Standardized Discriminant Coefficient**	*P Value*
Nonambulation	.784	<.0001
Metastatic neoplasm	.755	<.0001
Incontinence	.253	<.01
Divorced/separated marital status	.286	<.05
Age	.220	<.025

*No-code status was associated with the *presence* of a dichotomous characteristic (for example, incontinence) or with *increasing value* of a continuous variable (for example, age).

than CPR patients and nearly twice as many resided in a nursing home. The sex, racial-ethnic and formal religious compositions of the nonsurviving no-code and CPR groups were similar.

The mean number of diagnoses per patient was 5.5 for the nonsurviving no-code group and 4.5 for the CPR group (P not significant). A significantly greater proportion of nonsurviving no-code patients, however, had the diagnosis of neoplasm (23 of 37 versus 2 of 20 patients, $P<.001$) or dementia (13 of 37 versus 0 of 20 patients, $P<.01$). In all, 17 nonsurviving no-code patients and no CPR patients had a metastatic neoplasm ($P<.001$). No other statistically significant differences in diagnoses were found.

Through multivariable analysis,[10] nonambulation ($P<.0001$), metastatic neoplasm ($P<.0001$), incontinence ($P<.01$), marital status ($P<.025$) and age ($P<.05$) were found to be independently associated with a decision to withhold CPR (Table 3). These variables account for 61% of the variance in resuscitation status.

Discussion

Our observations suggest that on the medical service of at least one teaching hospital, no-code orders are not rare and, in cases of cardiac arrest, withholding CPR is more common than applying it. Because an active decision regarding resuscitation may not have been made for all patients, especially those not considered to be in danger of imminent cardiac arrest, our count of no-code orders may actually underestimate the prevalence of patients who would not receive CPR if they suffered a cardiac arrest.

In this setting no-code decisions were made by small groups that almost always included an intern and a resident and less frequently included the patient, family, attending physician, other physicians or nurses. Although attending physicians are legally responsible for patient care, they were often not involved in no-code decisions. House officers in this environment often function autonomously from attending physicians in making these decisions. For this reason specific measures, such as regulation or education programs, would assure greater involvement of the attending physician.

The variable participation of patients, even those who were oriented, mirrors the diversity of published no-code or treatment limitation policies for academic hospitals. Although some specify that the patient must play a preeminent role in this choice,[4,5] others appear to specify only a minimal role.[6] Because the mental state of many patients during hospital stay apparently precludes participating in the no-code decision, a policy recommending participation of in-hospital patients in no-code decisions would not be feasible for many patients in this and similar hospitals. Additionally, patients' families may not be available to participate in decisions regarding resuscitation. Thus, alternative guidelines for making decisions must be developed for cases in which patient or family participation is not possible.

The patient characteristics found to be associated with decisions made to withhold CPR in this study are consistent with factors previously hypothesized as considerations in limiting treatment, such as poor prognosis, excessive cost, patient refusal, a prognosis of poor quality of life,[11] diminished social value,[12] diminished capacity for social interaction,[13] lack of desire to live[14] or the burden of care. Given its nonexperimental design, however, the variables in this study are best described as characteristics of patients for whom CPR is not deemed appropriate, not as "causes" of no-code orders. We must learn if and how these characteristics are influential in the decision.

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The Ethical and Legal Framework for the Decision Not to Resuscitate

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Practicing physicians are frequently faced with the question of whether or not to institute cardiopulmonary resuscitation in case of cardiac or respiratory arrest in a patient in hospital. Medical training has usually not included any systematic analysis of this issue from either an ethical or a legal standpoint. Many physicians may be unaware that ethical and legal principles, as well as professional guidelines, exist to guide such decision making. In practice, physicians make this decision without the benefit of training in ethical analysis. The problem is especially acute in teaching hospitals when young physicians unacquainted with formal ethics or the law must often make decisions emergently. Studies show some discrepancy between ethical and legal principles and the actual decision making by physicians. For this reason, we recommend an approach that will enable physicians to make and implement decisions not to resuscitate that are consistent with current ethical and legal standards.

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After effective methods of cardiopulmonary resuscitation (CPR) were developed in the 1960s, it became standard practice to resuscitate any patient in hospital who had no pulse or respirations.[1,2] By the mid-1970s, however, there was increasing concern that attempting resuscitation of some in-hospital patients might be unduly invasive and offer little hope of altering their prognoses.[3] Several studies have shown that the fraction of resuscitated patients who are ultimately discharged from hospital ranges from 8.2% to 24%.[1,2,4-11] Because of the morbidity of CPR, the cost of subsequent intensive life support and the low long-term survival rate for certain patients, the routine application of these techniques in hospital has been called into question. Simultaneously there has been active discussion of a patient's right to die without technologic intervention in the setting of terminal illness.[12] The National Conference on Cardiopulmonary Resuscitation and Emergency Cardiac Care has expressed this concern:

> The purpose of CPR is the prevention of sudden, unexpected death. CPR is not indicated in certain situations, such as in cases of terminal irreversible illness where death is not unexpected. . . . It has even been suggested that resuscitation in some circumstances may represent a positive violation of a person's right to die with dignity.[13(p508)]

Physicians frequently face the problem of deciding for which patients it is advisable to withhold CPR. Medical education has in the past not included formal instruction in ethics or case law regarding these issues. As a result, many physicians feel uncomfortable and may not deal effectively with these situations.[14] We review the ethical and legal principles relevant to decisions not to resuscitate (also known as "no-code orders") and recommend a clinical approach to this problem derived from these principles.

Ethical Considerations

The principle of autonomy underlies the tradition, both ethical and legal, that rational persons have a right to self-determination based on their values and life plans. The principle of beneficence underlies physicians' fiduciary charge to do what, in their professional judgment, is best for patients.[15] Treatment that will reverse illness or restore health is considered best for a patient and therefore necessary. In a discussion of the ethics of the no-code orders, reversibility of the underlying illness is thus the basic medical question. Once a clinical judgment is made that a patient's death from the primary disease is inevitable, all treatments become, in a sense, elective.[15,16]

Competent patients may refuse treatment, including resuscitation, even when a physician feels that the underlying illness is reversible.[17] It is important to determine whether patients are in full command of their judgment when expressing these wishes. Patients who are severely depressed or in pain might wish for death but be thankful for life once the pain or depression is treated. We are not using "competence" in the legal sense of the term, but rather as a description of patients' ability to understand and to judge in a clinical setting. Determination of competence must often be made clinically because legal proceedings are often not possible nor are the subtleties of fluctuating consciousness included in adjudicated competency hearings. A careful examination of mental state, with attention to memory, mood, evidence of judgment and ability to abstract is regarded by many as enough to ascertain whether a person is mentally capable of consenting or refusing, if a question exists. If doubt remains, a psychiatrist should be consulted.[18] When a competent patient requests that resuscitation attempts be withheld, that wish should be honored, even if physician or family disagrees. If a condition is deemed medically

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irreversible but the competent patient requests that full resuscitative efforts be made, an order to withhold CPR should not be written. If major disagreements persist between patient and doctor or family, further discussions should ensue, in an attempt to resolve disagreements. In the end, however, the wishes of a competent patient should be honored.[19] If a physician feels that he or she cannot carry out the patient's wishes, it is advisable to help the patient find another provider. Rarely a patient with terminal illness in whom death is imminent may be in such psychologic distress that a discussion of CPR would be inhumane. In such a case, a physician may ethically decide to withhold CPR because it is contraindicated.

Special problems arise in the cases of patients unable to express their wishes because of coma, mental retardation, dementia or other alterations of consciousness caused by acute illness or drugs. Reversible causes of altered mental state should be sought and treated before consideration of an order not to resuscitate. If the mental incapacity cannot be treated, reversibility of the underlying illness, or medical prognosis, should be determined. This assumes a careful diagnostic evaluation, including appropriate consultations, before the decision regarding CPR can be made. A patient's clergyman or the hospital chaplain may be a useful consultant in this situation. Once the diagnosis and prognosis are determined, a physician must be guided by the duty to do those things that are likely to be of benefit to the patient.

Another ethical construct is the distinction between ordinary and extraordinary means to preserve life. Custom and common law require physicians to provide patients with reasonable and ordinary care consistent with contemporary standards of the medical profession. There is no common law duty to provide patients with extraordinary care, and such treatment may be withheld.[16] The distinction between ordinary and extraordinary has been debated at some length in medical, legal and philosophical literature, but one of the clearest accounts remains that of Kelly:

> *Ordinary* means of preserving life are all medicines, treatments, and operations, which offer reasonable hope of benefit for the patient and which can be obtained and used without excessive expense, pain, or other inconvenience. . . .
>
> *Extraordinary* means of perserving life . . . mean all medicines, treatments, and operations, which cannot be obtained without excessive expense, pain or other inconvenience, or which, if used would not offer a reasonable hope of benefit.[16(p122)]

Ordinary care, in this sense, does not mean customary care or community standard. Similarly, extraordinary is not synonymous with heroic. Rather, these definitions include nonmedical value considerations in the judgment of what differentiates ordinary versus extraordinary measures. In particular, it is a *patient's* determination of "reasonable" and "excessive" that carries the greatest weight. The controversy about whether CPR constitutes ordinary or extraordinary means of preserving life will be discussed.

Medical futility is a judgment involving considerable uncertainty. Reference to the literature and consultation with other physicians may help in establishing an accurate prognosis. Conditions that might be considered terminal and irreversible include untreatable cancer, end-stage cardiac, pulmonary or hepatic disease, progressive neurologic disorders and other progressive diseases for which therapy is ineffective and death is imminent.[15] An ethical problem arises because a physician's judgment of medical futility may be confounded by his or her evaluation of a patient's quality of life, value to society, age or cost of care. From an ethical standpoint, advanced age, mental disease or retardation and chronic disease that can be palliated should not, of themselves, be grounds for withholding CPR.[15] Life judged to be of poor quality by an observer may be quite satisfactory to a person living it. Such discrepancies may be especially great if an observer is young, healthy and able-bodied and the patient older, with chronic disease and mental or physical disabilities. In addition, a patient's own evaluation may change over time, as depression resolves or pain is relieved. Some authorities assert that quality of life can only be a decisive factor in the decision to withhold CPR if a patient's wishes cannot be known, the underlying condition is irreversible and all cognitive, sensory and interactive functions are absent or extremely deficient.[15]

The decision regarding resuscitation is further complicated by the family's wishes and the costs of medical care. These factors involve a potential conflict of interest. For example, the family may ask that a do-not-resuscitate order be written because of the emotional or financial burden of prolonged illness. Alternatively, they may request heroic measures to appease feelings of guilt or other psychologic needs arising from long-standing interpersonal dynamics. The family's wishes should be considered, but a physician's primary obligation is to the patient's welfare. There is pressure on physicians to function as "gatekeepers," to contain the cost of medical care to society by deciding who should and should not receive expensive care. Opinions on appropriate professional roles in this regard vary.[15,20] We are persuaded by the argument that a physician caring for an individual patient should offer to that patient those resources that are medically indicated.[15,16] Decisions limiting access to aggressive or intensive care because of age, diagnosis or other criteria are policy decisions that if necessary should be made on a societal level, where considerations of equity and justice apply.[21]

Legal Considerations

Many discussions of this issue appear in the legal literature, but few cases have actually addressed the question of orders not to resuscitate. One extreme view is that taken by Levin and Levin.[22] They argue that a person is not dead immediately after cardiopulmonary arrest in those states that recognize the brain death criterion and, therefore, that CPR initiated immediately after a cardiopulmonary arrest is ordinary and not extraordinary care in those states. They would hold physicians subject to criminal and civil liability for

depriving their patients of ordinary means of preserving life if they order that CPR be withheld without a patient's signed informed consent. This view is not generally accepted, however. Other legal authorities consider CPR to constitute extraordinary care in the case of a terminally ill patient and to fall outside the realm of care that a physician is required to provide.[23]

We have chosen three cases to illustrate the impact of court decisions upon this issue. Only the last, the case of Shirley Dinnerstein, directly addresses the legality of do-not-resuscitate orders. The other two cases have established relevant legal principles.

In 1976, the family of Karen Quinlan, a young woman in chronic vegetative state but being maintained on a ventilator, asked the court whether the patient could be disconnected from the ventilator. The New Jersey Supreme Judicial Court ruled that the ventilator support could be discontinued. This decision (1) affirmed the patient's constitutional right to refuse life-sustaining therapy, based on the right to privacy; (2) established the medical prognosis criterion—that is, the ventilator could be discontinued if there was no reasonable possibility of the patient returning to a cognitive, sapient state, and (3) designated the physician, the family and the guardian as the appropriate agents to apply the medical criterion. The court further stated that if the hospital ethics committee concurred with the prognosis, all parties involved would be immune from civil and criminal liability.[24,25]

The following year, a Massachusetts Supreme Judicial Court decision caused considerable controversy within the medical community. Joseph Saikewicz, a 67-year-old mentally retarded resident of a Massachusetts state hospital was found to have acute myeloblastic monocytic leukemia. He was a ward of the state. The court was asked whether chemotherapy should be administered to this person unable to give informed consent. The ruling was that chemotherapy, a life-prolonging but not life-saving treatment, should be withheld in this case. The decision affirmed the right of competent persons to refuse treatment, but stated that when a patient is terminally ill and incompetent, therapeutic decisions should be based on a judgment of what the patient would have wanted (substituted judgment). It upheld the withholding of extraordinary measures when there is no hope of recovery from the illness. Most controversial was its naming of the state's probate courts, rather than physicians or families, as the proper decision-making agents in such cases.[26-28] A number of articles in the medical literature criticized this mandate for court involvement in such therapy decisions.[29-33] The legality of ordering that resuscitation be withheld without a court sanction was unclear after the Saikewicz decision.[34] The following year, a case filed in Massachusetts tested that question.

Shirley Dinnerstein, a 67-year-old woman who resided in a nursing home, had progressive Alzheimer's dementia, a left hemiparesis as a result of a stroke, hypertension and coronary artery disease. She suffered from incontinence of urine and stool and inability to swallow without aspirating. Her personal physician recommended that she not be resuscitated in the event of a cardiopulmonary arrest. The physician and the patient's family asked the court whether a doctor might enter a "no code" order in a chart without judicial authorization, and if authorization were required, that it be given in her case. The court ruled that do-not-resuscitate orders may be written without approval of probate court in the case of an incompetent, terminally ill patient, and that the decision could be made by the physician and family. In the words of the court, "the law does not prohibit a course of medical treatment which excludes attempts at resuscitation in the event of cardiac or respiratory arrest and the validity of an order to that effect does not depend on prior judicial approval."[35] Some authorities insist that because of this ruling the family must agree to a "no code" order for an incompetent patient.[36] The Dinnerstein case is the only one to date specifically addressing the legality of no-code orders[37] and it has not been overturned. A case currently being investigated by a grand jury in New York challenges the withholding of CPR from two elderly in-hospital patients (R. Sullivan, "Medical aspects of decision making in resuscitation and life support," *NY Times,* September 19, 1982, p 1).

Establishing Guidelines

A physician is expected to exercise "the degree and skill of the average qualified practitioner, taking into account advances in the profession."[36] Uncertain about how the courts will treat do-not-resuscitate orders in the future, many medical groups, including hospitals and medical societies, have recently established formal guidelines for decisions not to resuscitate. These guidelines vary from institution to institution, but consistently address three issues: the competent patient, the incompetent patient and the procedure for implementing the decision.[38-41] Most guidelines affirm the need to follow a competent patient's wishes. They differ in the approach to the incompetent patient—that is, some hospitals require department chairpersons or hospital committees to be involved in the decision. Most require family concurrence if a patient is incompetent, but some state that the family's wishes are not legally binding unless a family member is legal guardian or conservator. Almost all guidelines require documentation in the progress notes of the factors leading to the decision, as well as conversations with consultants and family. All require a written doctor's order to withhold CPR.

The approach to orders to not resuscitate for physicians in training is slightly different than in practice. In a teaching hospital, where many providers care for a patient, responsibility for decision making is often diffuse. Guidelines developed for the University of Minnesota teaching hospitals recognize this distinction and require that an attending physician or chief resident be involved in the decision not to resuscitate.[40]

One common practice has been for physicians to tell nurses that a person is not to be resuscitated, but not

to write it as an order. This presents nurses with a significant communication responsibility, and no legal documentation. The "slow code," as it is called, poses a related problem for nurses. The clinician feels that resuscitation attempts would not benefit a patient, but is unwilling to make an explicit statement to that effect. The nursing staff is told to page the physician immediately rather than begin CPR or announce a full code. If nurses are not given a do-not-resuscitate order, they must initiate resuscitation attempts.[42] The likelihood of a good outcome is severely decreased by any delay in beginning CPR, thus a "slow code" cannot be justified. There is a substantial amount of literature on nursing malpractice and ethics establishing reasons why such practices are no longer acceptable in many hospitals.

Physician Factors

Although we may be guided by a sincere desire to follow a patient's stated or presumed wishes, there are many pressures that may interfere with adherence to our principles. It is often difficult to discuss a bleak prognosis with a patient. It is even more difficult to talk about a person's imminent death and to ask what his or her feelings are regarding CPR, defibrillation, intubation and mechanical ventilation. Our discomfort with such discussions may prevent us from exploring a patient's wishes.[18] Similar inhibitions may exist in discussing these questions with a family if the patient is unable to express his or her wishes. Strong feelings either for or against a no-code decision may be expressed by nursing staff or other people involved in caring for a patient.[18] Such feelings may be expressed verbally or nonverbally, and may influence our decision making. A physician may be tempted to withhold resuscitation attempts without consulting patient, family or other physicians.[18] Older patients and those with functional impairments may be more likely to receive a do-not-resuscitate order, as suggested by studies of physician behavior.[11,43,44] (See also the article by Uhlmann, McDonald and Inui in this mini-symposium.)

In another study decisions to discontinue CPR in emergency rooms were examined, in which 78 emergency room physicians were polled with case studies. Using age alone as a criterion, 4% of the respondents would cease CPR if the patient were older than 65 years and 9% would stop if the patient were older than 75 years of age. Regardless of diagnosis, if a patient were transferred from a nursing home, 18% would stop CPR. If a patient were senile, demented or mentally retarded, 54% would discontinue CPR. If a patient were described as having "end-stage" chronic obstructive pulmonary disease or malignancy, no further details given, 87% would stop.[11]

Pearlman and co-workers used a case study describing acute respiratory deterioration in an elderly male nursing home patient with chronic obstructive pulmonary disease to study the factors influencing physicians to decide for or against intubation. They found that whether they chose to intubate or not, respondents cited the following considerations in decreasing order of frequency: the nature of the acute problem; the patient's quality of life; the natural history of the disease; personal attitudes of the physician; inadequate information; previous courses in hospital; estimated survival time if intubated; impact of treatment on patient, family or society, and interpretation of patient and family treatment desires. Those who chose to intubate estimated a significantly longer life span than nonintubators. House staff withheld intubation significantly more frequently than did private practitioners.[43]

In a classic sociologic study, by polling 3,000 physicians with both case histories and attitude questions, Crane tested the hypothesis that physicians use information other than strictly physiologic criteria in deciding how aggressively to treat critically ill patients. This investigator found that age, the probability of mental or physical disability as a result of illness and the wishes of a patient all significantly influenced physicians to pursue a less aggressive course. In Crane's opinion, these findings represented a disparity between the traditional ethic of basing decisions only on prognostic biomedical criteria and the actual behavior of physicians. She recommended that guidelines be developed that outline both physiologic and social criteria for withholding or withdrawing treatment in specified conditions.[44]

The Symbolic Meaning of a Do-Not-Resuscitate Order

There is a tendency to equate deciding not to give CPR with deciding to stop all vigorous medical therapy directed at reversible processes. Some intensive care units have a policy not to accept any patients who carry do-not-resuscitate orders. A decision about resuscitation attempts can be made on the basis of the poor prognosis inherent after cardiopulmonary arrest in that patient. This does not necessarily imply that other aggressive measures are not indicated as long as a patient lives. At times it may be appropriate to withhold antibiotics or transfusions, but these decisions are distinct from the decision to withhold CPR. It also may be indicated in some patients to attempt certain limited measures in the event of cardiac arrest, but to desist promptly if they are not effective. The reversal of a relatively simple arrhythmia has a very different prognosis than more profound systems failure. This is not the same as the "slow code" because those measures used are instituted promptly in a vigorous manner and with a clear endpoint.

Even in dying patients, a do-not-resuscitate order does not imply less attentive care. One of the most unfortunate problems surrounding these decisions is the tendency of physicians to feel that a meaningful role is finished when we have decided to cease aggressive medical therapy. In fact, challenging therapeutic issues still exist. Orders should be reviewed and revised to maximize patient comfort. This may include intravenously administering fluids or giving oxygen or analgesia, or other interventions. Our involvement should be intensified by providing comfort measures

TABLE 1.—*A Stepwise Approach to Deciding Not to Resuscitate*

If patient is competent, honor patient's wishes
If patient is unable to understand condition or express wishes
Establish likelihood of reversing illness
If reversible, no do-not-resuscitate order
If prognosis unclear, no do-not-resuscitate order
If illness irreversible, a do-not-resuscitate order may be considered
Discuss decision with other physicians with expertise in establishing prognosis; physicians in training should discuss such decisions with attending physician or chief resident
Discuss decision with family, if available
If primary physician, consultants and family agree, a do-not-resuscitate order may be written; if significant disagreement exists, further discussions are indicated before recording a do-not-resuscitate order
If strong disagreement persists, a hospital ethics committee may be helpful in reaching a resolution

TABLE 2.—*Implementing a Decision Not to Resuscitate*

In progress notes, document the factors considered in the decision and the content of discussions with family and consultants
Write a doctor's order in the patient chart
Discuss the decision and the reasons for it with all staff involved in the care of the patient
Continue appropriate medical therapy and comfort measures
Reconsider the decision at regular intervals; the prognosis may change and, with it, a patient's code status

and by not abandoning a patient and family at a time of suffering and loss.

Conclusions and Recommendations

Based on a review of the ethical and legal literature on orders not to resuscitate, we have formulated a stepwise approach for physicians faced with such decisions (Table 1). A competent patient's wishes should be honored, under all circumstances, even when the physician disagrees. If a patient cannot express competent wishes, the physician must consider the reversibility of the illness. If the illness is reversible, a no-code order is neither ethical nor legal. If the prognosis is unclear, ethical and legal standards direct that no order should be written. Only when the process is irreversible does it become ethical to consider an order to not resuscitate. Under these circumstances, a physician must discuss the decision with other physicians. Physicians in training should consult with an attending physician or chief resident. These consultations are essential to verify prognosis and re-evaluate decisions that may not be in a patient's best interest. The family's wishes should be sought. If all agree, a do-not-resuscitate order may be written. If disagreement exists, the discussion should continue. If disagreement persists between a physician and family, it is in general prudent not to write a do-not-resuscitate order, despite the opinion of some authors who consider the family's wishes in this instance to be less binding than the wishes of a competent patient.[45]

Some philosophers feel that physicians are not qualified to make these critical and complex ethical decisions, and would defer to ethics committees or to the courts.[46] While *Dinnerstein* established that physician and family concurrence justifies such a decision on behalf of a clearly incompetent patient, subsequent challenges to this precedent may occur. In the most difficult cases—either of disagreement between family and physician, or of questionable patient competence—there is no consistent legal recommendation. If significant uncertainty surrounds the decision for a particular patient, it is ethically proper and consistent with medical tradition to err on the side of attempting resuscitation.[17,25] In especially problematic cases, or where a patient is a ward of the state, judical intervention may be warranted.

The implementation of a no-code order must also follow ethical and legal guidelines (Table 2). It is essential to document the factors leading to the decision, as well as the content of discussions with the family and consultants in the progress notes. An order should be written. It is important to discuss the decision and the reasons for it with all staff involved in caring for the patient. The distinction between withholding CPR and withholding other forms of therapy should be addressed case by case. An order not to resuscitate should be re-evaluated at reasonable intervals. Patients may unexpectedly improve, and a no-code order may need to be withdrawn.

Once the decision has been made not to attempt resuscitation and to allow a terminal illness to take its course, a significant challenge remains to a physician: "Even when we decide that our advanced technologies are no longer indicated, we can still agree that certain extreme measures are indicated—extreme responsibility, extraordinary sensitivity, heroic compassion."[18(p574)]

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Noninvasive Muscle Stimulators

QUESTION:

Is the home use of noninvasive muscle stimulators for the prevention of muscle atrophy considered accepted medical practice?

OPINION:

In the opinion of the Scientific Advisory Panels on Neurology and Physical Medicine and Rehabilitation, noninvasive muscle stimulation is of proved value in retarding atrophy and promoting nerve regeneration. This procedure has been accepted medical practice for many years for such conditions as Guillain-Barré syndrome, facial nerve palsy and incomplete lesions of peripheral nerves. Its use to prevent muscle atrophy in patients with multiple sclerosis, spinal cord injuries and head injuries is still considered investigational. Whether noninvasive muscle stimulation actually improves long-term functional recovery is still undetermined.

Home use of noninvasive muscle stimulators by persons other than physicians or therapists raises some potential problems, such as the hazards of accidental electrical injury or damage to tissue. However, home use of noninvasive muscle stimulator can be considered accepted medical practice if the person operating the device is instructed in its proper use by a physician or a therapist knowledgeable in the motor points of muscles.

Special Article

Prospective Pricing and DRGs

STEPHEN LEWIS, *San Francisco*

Even before Medicare's Prospective Payment System (PPS) for hospitals went into effect, it was already a cliché that the new system was the most significant change since the program's inception. More important, PPS may become the model for similar payment schemes involving private sector payers and covering physician and outpatient services as well.

Under PPS a hospital is paid a fixed, predetermined price for a Medicare inpatient case, based on the patient's Diagnosis Related Group (DRG). If the hospital's actual costs for treating that patient are below the DRG price, the difference is retained; if its costs are higher, the hospital absorbs the loss. This new element of risk reverses the hospital's traditional incentive to maximize its costs; now, the hospital and physician must work together to minimize them.

Prospective Pricing—The Basics

Prospective pricing is nothing new. Health maintenance organizations (HMOs) and other capitated plans have always used prospective pricing and payment,* and some hospital rate review programs also involve prospective pricing. The concept is implemented in a number of different ways, but two basic elements seem to occur in all prospective pricing systems: the payment unit and the unit price.

The payment unit is the unit of service on which the price is based. It may be highly discrete, like a simple x-ray study. Moving away from this extreme the payment unit may be somewhat more aggregated. The hospital's daily room charge, for example, aggregates food service, basic nursing, housekeeping and many other services. More aggregated units would be the all-inclusive per diem rate, per discharge, per capita, and so forth. The most highly aggregated unit in current use would be statewide budget review, a single unit combining the total operating budgets of all hospitals in a particular state. Conceptually, of course, the same notion could be applied at the national level.

*Prospective *pricing* refers to a predetermined price or fee, while prospective *payment* means payment in advance of the provision of services. Thus, Medicare's PPS is something of a misnomer in that actual payment is still retrospective. HMOs, by contrast, are truly paid prospectively.

Whatever the payment unit, a corresponding unit price is established. Just as the unit falls somewhere along a continuum of aggregation, unit price can be thought of as falling on a continuum of provider control. At one extreme the price is simply negotiated, and the only limits to the provider's control over price are those of his or her negotiating strength vis-à-vis the payer. The provider has slightly less control when the price is based on his historic costs, and even less if his costs are calculated in with those of other providers. At the farthest theoretical extreme from the negotiated price is that imposed unilaterally by the payer.

Implicit in this discussion is a parallel between these two elements. A highly aggregated unit of service, such as a regional or state cap on combined revenues, tends to coincide with a high degree of payer control over the unit price, and vice versa. A third relevant variable is the degree of cohesiveness among payers; the more payers that participate, the less negotiating room a provider has. The Health Care Financing Administration (HCFA), for example, is the only payer currently participating in PPS, and hospitals with only a small inpatient Medicare census will be only slightly affected by the system. In New Jersey, however, all third-party payers participate in the state plan, so hospitals have substantially fewer options for negotiating and for shifting cost from one class of payer to another.

The Rationale—Cost Containment

To the degree that it transfers control over the price of health services from the provider to the payer and informs the provider of the revenue limits imposed by that control, prospective pricing is in theory a means of reducing the growth rate in health care costs.

At the hypothetical extreme of payer control, all payers (both public and private) would jointly allocate a fixed amount of revenue among all providers, leaving each provider completely at risk for cost overruns. Without a means of shifting costs, negotiating a higher unit price or modifying the all-inclusive units of payment, the provider would have no choice but to hold costs below revenue allocation. In practice none of

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ABBREVIATIONS USED IN TEXT

DRG = Diagnosis Related Group
HCFA = Health Care Financing Administration
ICDA-8 = International Classification of Diseases Adopted—8th Revision
ICD-9-CM = International Classification of Diseases—9th Revision—Clinical Modification
LOS = length of stay
MDC = major diagnostic category
MEDPAR = Medicare Provider and Analysis Review
PPS = Prospective Payment System
TEFRA = Tax Equity and Fiscal Responsibility Act of 1982

the prospective systems in the United States represents this degree of one-sided payer control; in the relatively free market of American health care, market forces strike a balance between the payer's and provider's interest. Nonetheless, to the extent a given prospective system places control in the payer's hands, it increases the provider's financial risk and gives an incentive to minimize costs.

A second major element also contributes to the provider's cost containment incentive. Advance knowledge of the unit price and the degree of aggregation in the unit tells the provider the extent to which the prospective prices constitute a de facto revenue cap on his or her operation. This knowledge provides a cost target that must be met, at least in the long run, if the provider is to remain economically viable. It also suggests what revenue maximizing strategies, if any, are feasible.

The payment unit under PPS is the case-mix-adjusted discharge. This suggests two limiting factors or revenue maximizing options: for low-cost hospitals it suggests that net revenue can be increased by encouraging more Medicare inpatient admissions (but not if they preclude admitting higher paying private sector patients). For high-cost hospitals, the decision of whether to discourage Medicare admissions will be influenced by the proportion of costs the PPS rate covers. If PPS pays more than the variable cost of each stay, then perhaps a hospital should *encourage* such admissions even at a loss because they contribute to meeting fixed cost; the more admissions, the less the total loss will be. If PPS does not meet the hospitals' variable *or* fixed costs, then the hospital should probably discourage Medicare admissions.

Case mix can also be employed in a revenue-maximizing strategy. For most hospitals, some DRGs will be profitable and others will not. Hospitals will thus seek admissions in the profitable services and try to avoid the "loss leaders."

Generally speaking, the less aggregated the payment unit and the fewer or smaller the participating payers, the more options a provider has for maximizing net profit by increasing revenue. Conversely, a highly aggregated payment unit and unified payers (or a single dominant payer) tend to make the prospective system a revenue cap or ceiling. Under these conditions the profit maximizing strategy essentially becomes one of reducing costs. In real life, most prospective systems lie between these extremes so the appropriate strategy is a combination of cost reduction and revenue maximization. From the provider's prospective, it does not particularly matter which approach is emphasized, as long as the optimal result is achieved.

To a payer, however, the difference between provider strategies is crucial; a revenue-maximizing strategy on the provider's part is potentially costly for the payer, so the payer has a major interest in giving providers an incentive to emphasize alternative strategy, the cost-reducing approach. The commercial health insurance industry recognizes this, and has launched a major campaign to encourage all-payer prospective systems at the state level. These systems would not only protect commercial carriers from providers' shifting costs they cannot recoup under PPS but also, by presenting a united front, the payers would force providers to reduce costs to all payers in the aggregate. The federal government has facilitated this effort by establishing criteria for state prospective systems which, if met, would obligate Medicare and Medicaid to participate. These criteria were included in the Social Security Amendments of 1983, which established PPS.

There is strong precedent for private-sector payers following the lead of Medicare in determining coverage and payment policies. Given the large investment required for providers to comply with PPS requirements, it seems likely that PPS will be a model for all-payer systems that develop and for any expansion into outpatient and for physician services. Thus, a closer look at the mechanics of the new federal system is in order.

PPS and Diagnosis Related Groups

Background

In its simplest terms, PPS is a system for prospectively setting prices for Medicare inpatient services. The payment unit is the "case" or, in practice, the case-mix-adjusted discharge. The unit price is based on aggregate hospital costs nationwide, and the case-mix adjustment to the payment unit is based on a cluster of case-specific variables that assign the patient to a particular Diagnosis Related Group.

HCFA has been experimenting with prospective pricing since the late 1970s, participating in a variety of state and regional programs. In some of these HCFA has taken a leading role as an initiator or payer. In other programs, initiated either by state governments or regional entities, HCFA's role has been limited to granting waivers of the rules of Medicare participation.

Probably the best known and, as it turns out, the most influential HCFA experiment in prospective pricing has been the New Jersey program. Although this system is administered by the state and involves private sector payers as well, Medicare was a prime mover in initiating and developing the DRG-based system that in large part provides the model for the national PPS that went into effect in October 1983.

The New Jersey PPS illustrates two characteristics

that are likely to dominate such programs in the near future: (1) the DRG methodology for determining payment unit and (2) the integration of government payers into an all-payer state-level system. To the extent private sector payers have tended to follow HCFA's lead in determining their reimbursement policies, it appears likely that federal endorsement of the DRG methodology will establish it as the dominant payment mechanism for prospective systems nationwide. This likelihood is increased by participation of private sector payers of New Jersey. As private sector payers in other states increase their pressure for prospective systems, they will naturally look toward the New Jersey program as their model.

In terms of the basic PPS elements described above, the New Jersey system involves a case-mix-adjusted discharge as the unit of payment and a statewide cost-based payment formula which calculates fixed and variable costs separately (as a method to provide an incentive to refrain from unnecessary admissions). The key to implementation of this system is the diagnosis-related group, or DRG. DRGs are the means by which the system provides the standardized or uniform payment unit which can be adjusted to fit an institution's specific case mix. Its primary power lies in the fact that control of payment is not in the hands of providers, but neither are providers penalized for treating costly cases. Thus, in theory at least, DRGs remove incentives for providers to attempt to maximize their own incomes by behavior that is less than optimally cost effective. In practice there are, of course, limitations to the ability of DRGs to perform this function. Nevertheless, HCFA asserts that it is satisfied with the performance of DRGs in providing for a rational, cost-effective payment system.

Diagnosis Related Groups

The first set of Diagnosis Related Groups was developed at Yale University in the late 1960s for use as a hospital management tool. It was not originally intended for use in a payment system, but rather for utilization review purposes to identify abnormal lengths of stay and as a means for the hospital to identify service areas which were relatively more or less cost effective for the hospital to provide.

Development of the DRGs was done in two stages. Initially, a panel of clinicians sorted the diagnostic and procedural codes from the *International Classification of Diseases Adopted—8th Revision (ICDA-8)* into major diagnostic categories (MDCs). More than 10,000 codes were clustered into 83 MDCs. The criteria for this grouping process were (1) consistency of anatomic classification or the manner in which patients were clinically managed, (2) a sufficient number of patients within each MDC for statistical analysis and (3) coverage over the complete range of codes without overlap. Once the set of MDCs had been established, a sample of more than 700,000 medical records was drawn from approximately 170 hospitals in New Jersey and Connecticut. These records were grouped into the various MDCs, based upon the principal diagnosis or manner of treatment indicated on each record. Each record was assigned to only one MDC.

After the medical records had been assigned to their respective MDCs, the records within each individual MDC were subjected to a form of factor analysis. The objective of this procedure was to identify characteristics in a medical record which accounted for the variation in the length of stay among the records included in each MDC. It evaluated variables such as patient age, sex, manner of treatment (medical or surgical) and the presence or absence of complications (conditions appearing during hospital stay) or comorbidities (conditions present at the time of admission).

The results of the factor analysis indicated that the importance of a particular variable in explaining variance in length of stay was different from one MDC to another. Thus, in some MDCs the age variable, for example, was significant only if dichotomized (age 0 to 69, 70 and above), while in other MDCs it was significant only if divided into three groups (0 to 17, 18 to 69, 70 and above), while in still other MDCs age was not a significant variable at all.

These findings were used to generate a set of subgroups within each MDC. These subcategories became the now-famous DRGs. Within each individual MDC, a branching logic was used based on the relative importance of each variable in explaining the variance in length of stay (designated as LOS). To take a hypothetical example, if in an MDC the surgical versus medical mode of treatment was the most significant variable, dichotomized age the second most significant, the presence of comorbidity or complications the third most important variable and none of the other variables appeared significant, then that particular MDC would include eight DRGs: two treatment modes (medical and surgical) times two age categories times presence or absence of comorbidities. This classification allowed assignment of any individual case, based on its medical record, to one and only one DRG. Given that the factors differentiating between DRGs are chosen on the basis of their ability to explain differences in length of stay, each DRG is assumed to be homogeneous in terms of LOS within that individual DRG. LOS in turn is used as a proxy for the amount of resources used in treating the cases included within that individual DRG.

In summary, the first stage of DRG development was intended to insure that the final groups are "clinically coherent" in the sense that they represent similarities among bodily systems treated or in case management, while the second stage, the subcategorization of MDCs into DRGs, was intended to insure that the groups are similar in terms of resource consumption. The result of this effort was the division of the 83 MDCs into 383 DRGs.

Working with Yale and the state of New Jersey, HCFA began gradual implementation of its experimental PPS based on DRGs. From the start, there were allegations of problems stemming from this system.

Among the major problems alleged were (1) that DRGs were developed with regional data (New Jersey) and therefore reflected local practice patterns, (2) that different data bases or different development teams might produce a different patient classification, (3) that the system was not clinically coherent and was difficult to use by doctors and hospital administrators, (4) that DRGs were based on LOS rather than on direct measures of cost (LOS was questioned as to being a good proxy for resource use, and DRGs still had wide variability of LOS within individual DRG categories), (5) that because the presence of any secondary diagnosis placed the patient in a higher-cost DRG, patient assignments to the DRGs could be easily manipulated or "gamed" (similarly, assignment of patients to DRGs was affected by the order in which surgical procedures were listed, and DRGs used the first procedure listed, which was not necessarily the most important from a resource-use perspective), (7) that there were too many "other" groups (each of the 83 MDCs had an "other" or catchall group) and (8) that the system was insensitive to difference in level of severity of illness within a DRG (no direct measure of severity was included in the development of DRGs).

In response to these criticisms, and because *ICDA-8* had been superseded by the *International Classification of Diseases—9th Revision—Clinical Modification (ICD-9-CM),* HCFA awarded a grant to Yale in 1979 to develop a new set of DRGs specifically geared to the requirements of the New Jersey PPS. The new DRGs were intended to be (1) medically interpreted, (2) based on information available in existing medical record abstracts (for example, uniform hospital discharge data set), (3) limited in number (fewer than 500 DRGs), (4) compatible with Medicare data for eventual HCFA use, (5) limited in variation of LOS within a DRG, (6) based on explicit rules on how to subdivide an MDC, (7) of sufficient size (in numbers of patients) to permit comparative analysis across hospitals and (8) representative of the entire range of hospital patients.

The development of the new DRGs became a large-scale project, including researchers, clinical consultants, a management review committee representing scientists from federal and state agencies and universities and a separate review structure of clinical consultants from New Jersey. The procedure followed was essentially the same as that employed in developing the original MDCs and DRGs, with some important exceptions. The 23 new MDCs were based primarily on organ systems because this structure parallels that of the medical specialties, which in turn influences practice patterns. Where body systems are not the identifying characteristic of an MDC (such as MDC 15, newborns and other neonatal conditions originating in the perinatal period), the MDCs still differentiated from others along specialty lines. Another major difference from the original set of DRGs is that within any new MDC the primary factor assigning a case to a particular DRG is the question of whether a surgical procedure was carried out. This reflects the relatively high cost of surgical versus nonsurgical treatment.

In response to the criticisms of the original set, a national data base of approximately 250,000 cases was used in development of the new DRGs and an additional 1.15 million records were used to test them. Replicability was improved by applying a set of explicit rules in developing the DRGs and was tested by having three different teams develop DRG definitions, which turned out to be substantially similar. The organization of MDCs along medical specialty lines is expected to improve clinical coherence and the relationship of LOS to costs was validated by a comparison between LOS data and New Jersey cost data. The opportunity for "gaming" is reduced by a new hierarchy of surgical procedures which insures that only the major surgical procedure is the basis for assignment of a particular case to a DRG. No specific effort was made to allow for variations in severity, because research indicated that variation in cost tended to be affected more by differences in practice patterns than by differences in level of severity.

The new DRGs were released in early 1981 for use in the New Jersey PPS. These are the DRGs that will be employed in the national system when it is implemented.

As the cost of Medicare has grown at an accelerated rate in recent years, HCFA has investigated a wide range of cost containment strategies. Among these options, prospective pricing is attractive because of its perceived track record of demonstrated effectiveness, its equity among providers, relative ease of implementation, and its political acceptability to the large numbers of voting Medicare recipients. It seems intuitively obvious that if provider incentives have been a major driving force in Medicare inflation, as they are widely perceived to be, the reversal of those incentives should be an extremely effective cost containment device. HCFA interprets the low Medicare inflation rates in states with prospective pricing relative to the country as a whole as evidence of the success of such programs. Adjusting payment for an individual provider's case mix is seen as a method to guarantee equitable payments among providers without giving providers themselves control over the level of payment. Existing demonstration projects provide a model for implementation and the lack of any apparent increased burden on patients is considered unlikely to arouse opposition among Medicare recipients.

A direct impetus for Medicare PPS was the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA) Among its wide-ranging provisions, this law (1) established per-case caps for individual hospital reimbursement under the existing retrospective system and (2) required HCFA to develop a proposal for a prospective nationwide payment system. The payment cap, known as "target" rates, included some elements of prospective pricing. Primary among these was the feature of provider risk for costs incurred above the payment ceiling. The case-mix adjustment in this system

involved the use of DRG data, but because the formula was based on the individual hospital's historic costs there was no incentive for a relatively inefficient hospital to improve its cost effectiveness relative to other institutions. Moreover, the risk incentive was weak. Hospitals that incurred cost overruns were penalized only half of the overage, while the more cost effective hospitals were permitted to retain only half of the savings achieved.

The TEFRA target system was implemented October 31, 1983, and is being used during the phase-in period of the PPS to help determine the hospital-specific portion of the payment formula. Even after the PPS has been fully implemented the TEFRA targets will be used to determine payment for those institutions exempted from PPS.

It was the second PPS-related provision in TEFRA that has had the greater impact on the Medicare system. TEFRA directed the Secretary of Health and Human Services to recommend a plan for a Medicare PPS. Approximately two months after the passage of TEFRA, Secretary Richard Schweiker proposed a DRG-based system to Congress for the Social Security amendments of 1983 (HR 1900) signed by President Reagan in April. This established a time frame of less than six months for implementation of the most major reform in Medicare's history. From the tight time frame involved and the tone of Secretary Schweiker's statements to Congress, it appears that the choice of a DRG-based system was to some degree a matter of expedience. Schweiker acknowledged that higher levels of aggregation could have achieved greater cost containment, but also noted that the DRG model was the only practically tested paradigm that could be implemented within what he considered a realistic period.

Mechanics of the Medicare PPS

Under HCFA's system, DRG will be the payment unit and unit price will be based on a nationwide measure of hospital costs. Each DRG will be assigned a weight analogous to the unit values assigned to procedure codes in the California Workers' Compensation Fee Schedule, and that weight, multiplied by the unit value, will determine the payment for the individual case.

The DRG Relative Price Index, the weights attached to individual DRGs, are based on the Medicare Provider Analysis Review (MEDPAR) data file which consists of information regarding billed charges and clinical characteristics, such as principal diagnosis and principal procedure, for a 20% sample of all Medicare short stay hospital bills submitted in a one-year period. The charge data are used to determine the relative cost of each DRG compared with the "average" DRG. The hypothetical average DRG is assigned an index value of 1.0 and the 467 actual DRGs range above and below that value. DRG 001, for example, craniotomy, has an index value of 3.5, indicating that the typical cost for a craniotomy case is approximately three and a half times that of the hypothetical average case.

The unit price or National Representative Cost Per Discharge is found by combining Medicare cost reports and hospital discharge files for the same year as the MEDPAR file employed in determining the relative DRG price index. The most recent year for which complete data are available is 1981, so 1981 figures adjusted for inflation and regional cost differences will be used. The hospital's Medicare cost report provides detailed audited information about allowable costs incurred by institutions, while discharge files provide accurate counts of the number of discharges. The cost data divided by the number of discharges provides a flat cost per discharge which, combined with the Relative DRG Price Index or Weights, provides a national standard price for each DRG. The Medicare cost reports also provide information on those costs which are not calculated into the DRG formula but passed through directly on a retrospective basis.

The foregoing is a simplification of the way in which DRGs will be used to determine hospital payment after the PPS has been fully implemented. A gradual phase-in began October 1, 1983, with each hospital beginning implementation at the start of a new Medicare reporting period. While many hospitals began October 1, others began January 1 and a few will begin as late as July 1, 1984. Over the course of the next three years the basis of payment will shift from 75%-hospital-specific, 25%-DRG, to 25%-hospital-specific, 75%-DRG. Within the DRG portion, the regional cost basis will gradually be dominated by the national DRG rates. The changes in regional-federal mix occurred October 1, regardless of the hospitals' reporting period. Thus, the exact mix of the three components will vary among hospitals at any particular time during the transition period.

Exceptions and Allowances

In a program as complex as Medicare, there are obviously going to be exceptions to a standardized payment system. Using the term "exceptions" generically, exceptions to the PPS fall into three broad categories: service exceptions, institutional exceptions, and cost exceptions.

Service exceptions refer to those services covered by Medicare but which will continue to be reimbursed under the retrospective system. The most obvious areas of service exemptions from PPS are physician services billable under Part B and ambulatory hospital services. This means that the PPS will at least initially be restricted to inpatient physicians defined in TEFRA as being included under Part A—that is, services that cannot be billed to an individual patient.

Institutional exceptions include long-term, pediatric, rehabilitation and psychiatric hospitals which will continue to be reimbursed for inpatient services under the retrospective cost-based TEFRA targets. Veterans hospitals and those under demonstration or state all-payer programs are also excluded. Hospitals designated as sole community providers, particularly in rural areas

in western states, will be included under PPS but will be given special allowances for costs such as maintaining the availability of emergency facilities on a 24-hour basis. To some degree, this allowance is also intended to serve as compensation for the fact that the DRG-based system tends to be biased in favor of large-scale providers in that it assumes a large enough body of cases for the "law of large numbers" or averaging effects to neutralize the impact of extreme cases.

Cost exceptions include pass-throughs on a retrospective basis of capital costs and direct education costs with a single lump sum allowance for indirect education costs. This lump sum would be calculated individually for each teaching hospital, based on the proportion of Medicare costs to its total teaching overhead.

All of these exceptions will be in effect during the three-year phase-in period, but HR 1900 mandated that the Department of Health and Human Services (DHHS) study the feasibility of eliminating several of them soon. Among these the most potentially important are physician services billable under Part B but rendered to hospital inpatients in institutions covered by the DRG system, capital costs and long-term care facilities. Interestingly, there is some Congressional support for legislation to implement the inclusion of physician services even before the DHHS study begins.

Health maintenance organizations will have two options for payment after PPS has gone into effect. HMOs may either go at-risk on a capitation basis paid at 95% of the average area per capita cost (AAPCC) or, alternatively, may be paid on a reasonable cost-per-case basis at the PPS rates. In New Jersey, HMOs have complained that LOS-based DRG rates discriminate against them since they already achieve a lower LOS than retrospective payers, but put the savings into a broader benefits package.

A combined service-cost exception is the outlier, special supplemental allowances for cases which have unusually long LOS or high costs. Outliers were introduced into the New Jersey system to satisfy self-pay patients who had short hospital stays or low-cost stays and resented "subsidizing" more expensive patients. Under Medicare, if a case exceeds a set cutoff point or threshold for its DRG in terms of cost or LOS, it receives a supplementary payment DRG rate divided by the mean LOS for that DRG, multiplied by the number of days beyond the cutoff point. Cost outliers are cases that do not exceed the LOS cutoff but do go beyond a cost threshold. While LOS outliers are automatically identified, a cost outlier must be requested by the hospital and is subject to medical review. In order to minimize the hospital's incentive to generate outliers, payment will be at only 60% of the prorated DRG amount.

Summary

Prospective pricing seeks to contain health care costs by increasing the payer's control over the level of expenditures. Its two basic elements are (1) a highly aggregated payment unit, which minimizes the providers' ability to manipulate utilization and (2) a predetermined, known unit price. By constraining utilization and placing providers at risk, prospective pricing stimulates the providers' incentive to maximize operating margins by reducing costs rather than increasing gross revenues.

The DRG-based prospective pricing system (PPS) introduced into the Medicare program may soon be replicated in the private sector via state all-payer plans. In any event, it very probably will be applied to Medicare reimbursement of ambulatory, long term and physician services.

In Memoriam

California Medical Association

Beatty, John H., Berkeley. Died August 15, 1983, aged 66. Graduate of Washington University School of Medicine, St Louis, 1941. Licensed in California in 1946. Dr Beatty was a retired member of the Alameda-Contra Costa Medical Association.

Bigler, Mary F., Freedom. Died July 22, 1983, in Watsonville, aged 83. Graduate of the University of Minnesota Medical School, Minneapolis, 1927. Licensed in California in 1927. Dr Bigler was a retired member of the Los Angeles County Medical Association.

Burns, Lafayette E., Rolling Hills. Died August 2, 1983, aged 56. Graduate of George Washington University School of Medicine, 1955. Licensed in California in 1956. Dr Burns was a member of the Los Angeles County Medical Association.

Colman, Arnold L., San Francisco. Died September 17, 1983, in San Francisco, aged 52. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1955. Licensed in California in 1956. Dr Colman was an associate member of the San Francisco Medical Society.

Corey, Hope M. H., Burlingame. Died August 3, 1983, aged 57. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1951. Licensed in California in 1951. Dr Corey was an associate member of the San Francisco Medical Society.

Deamer, William C., San Francisco. Died September 16, 1983, in Yugoslavia, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Dr Deamer was a member of the San Francisco Medical Society.

East, Norman R., Redwood City. Died August 22, 1983, in San Mateo of myocardial infarct, aged 64. Graduate of the University of Texas School of Medicine, Galveston, 1943. Licensed in California in 1948. Dr East was a member of the San Mateo County Medical Society.

Greenman, Robert Alvin, Jr, Templeton. Died July 14, 1983, in Atascadero, aged 59. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1949. Licensed in California in 1950. Dr Greenman was a member of the San Luis Obispo County Medical Society.

Grimaud, Harry J., North Hollywood. Died June 13, 1983, aged 63. Graduate of Northwestern University Medical School, Chicago, 1946. Licensed in California in 1947. Dr Grimaud was a member of the Los Angeles County Medical Association.

Hogstrom, James L., Fortuna. Died July 10, 1983, in Fortuna, aged 35. Graduate of the University of Wisconsin Medical School, Madison, 1969. Licensed in California in 1974. Dr Hogstrom was a member of the Humboldt-Del Norte Medical Society.

Rivera, Gabriel Alfonso, Los Angeles. Died June 1, 1983, aged 79. Graduate of Washington University School of Medicine, St Louis, 1929. Licensed in California in 1930. Dr Rivera was a retired member of the Los Angeles County Medical Association.

Rose, Milton, Palo Alto. Died August 8, 1983, in Palo Alto, aged 80. Graduate of Yale University Medical School, New Haven, 1935. Licensed in California in 1944. Dr Rose was a member of the Santa Clara County Medical Society.

Rosenberg, Rudolph, San Pedro. Died July 9, 1983, aged 72. Graduate of Rush Medical College, Chicago, 1937. Licensed in California in 1946. Dr Rosenberg was a retired member of the Los Angeles County Medical Association.

Skinner, Larry D., Placerville. Died July 16, 1983, in Sacramento of myocardial infarct, aged 36. Graduate of the University of Nebraska College of Medicine, Omaha, 1973. Licensed in California in 1974. Dr Skinner was a member of the Sacramento-El Dorado Medical Society.

Smiley, Stanley J., Carmichael. Died July 21, 1983, in Reno, Nevada, of carcinoma, aged 64. Graduate of George Washington University School of Medicine, Washington, DC, 1943. Licensed in California in 1944. Dr Smiley was a member of the Sacramento-El Dorado Medical Society.

Idaho Medical Association

Hoss, Glenn Arthur, Twin Falls. Died August 31, 1983, in Twin Falls, aged 68. Graduate of the University of Illinois College of Medicine, Chicago, 1941. Licensed in Idaho in 1941. Dr Hoss was a member of the South Central Idaho District Medical Society.

New Mexico Medical Society

Boyd, Olin B., Alamogordo. Died April 20, 1983, in Alamogordo, aged 82. Graduate of St Louis University School of Medicine, St Louis, 1928. Licensed in New Mexico in 1933. Dr Boyd was a retired member of the Otero County Medical Society.

Utah State Medical Association

Amano, Joseph, Clearfield. Died July 29, 1983, in Ogden, aged 57. Graduate of the University of Utah College of Medicine, Salt Lake City, 1955. Licensed in Utah in 1956. Dr Amano was a member of the Davis County Medical Society.

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

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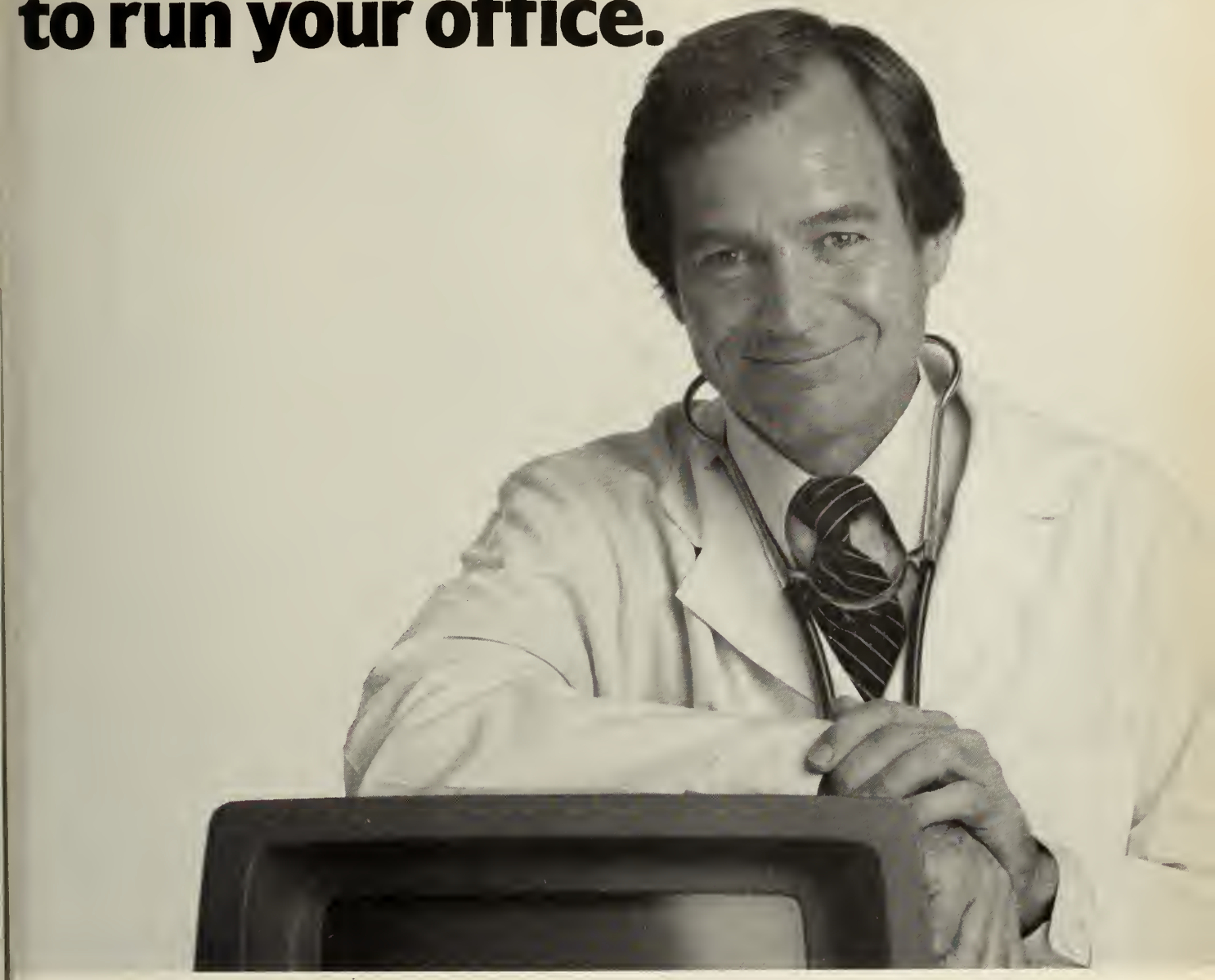

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(Continued from Page 25)

April 11—**Cardiac Emergencies.** LLU. Wednesday. 4 hrs. $50.

April 12-14—**Current Emergency Diagnosis and Treatment.** UCSF. Thursday-Saturday. 16 hrs. $260.

April 14-21—**Problems and Controversies in Emergency Medicine.** UCSD and Scripps Memorial Hospital, Encinitas at Maui. One week. 21 hrs. $335. Contact: UCSD.

April 30-May 4—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday.

May 5-6—**1st Annual Emergency Symposium.** Southern California Kaiser-Permanente Medical Group at Century Plaza Hotel, Los Angeles. Saturday-Sunday. 11 hrs. $150. Contact: Dept. of Clinical Services, SCKPM Care Program, 4747 Sunset Blvd., Los Angeles 90027.

May 21-22—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

INTERNAL MEDICINE

January 16-20—**2nd Biannual Gastrointestinal and Hepatic Diseases Conference.** Honolulu Medical Group Research and Education Foundation at Mauna Kea Beach Hotel, Hawaii. Monday-Friday. 20 hrs. Contact: Yvonne Brewer, MPH, Education Director, HMGREF, 550 Beretania St., Honolulu, HI 96813. (808) 537-2211, ext. 751.

January 19-21—**American Society for Gastrointestinal Endoscopy Meeting** at San Francisco. Thursday-Saturday. 16 hrs. Contact: Mr. William T. Maloney, Executive Director, ASGE/PG, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

January 19-21—**Dual Brain.** UCLA. Thursday-Saturday. 26 hrs. $160.

January 26-28—**Alzheimer's Disease: Toward Clinical Management.** Annenberg Center for Health Sciences, Rancho Mirage. Thursday-Saturday. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 340-3911.

February 3-4—**Current Problems in Clinical Endocrinology.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. Contact: Dianne Tisue, Conference Coordinator, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 8—**Diagnosis of Acute and Chronic Abdominal Pain.** LLU. Wednesday. 4 hrs. $50.

February 8-10—**17th Annual Recent Advances in Neurology.** UCSF at Fairmont, San Francisco. Wednesday-Friday.

February 10-18—**Topics in Internal Medicine.** UCSD. One week.

February 11-12—**Diabetes—New Horizons in 1984, A Clinical Update.** The Cypress Foundation, Northern California Affiliate American Diabetes Association and Monterey County Medical Society at Holiday Inn, Carmel-by-the-Sea. Saturday-Sunday. 10 hrs. Contact: Cypress Fndn., P.O. Box 80308, Salinas 93912. (408) 455-1833.

February 13-24—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

February 17-19—**Mind and Metabolism: Regulation and Self-Regulation of the Autonomic and Central Nervous System.** UCLA. Friday-Sunday.

February 17-18—**Infectious Disease.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

February 23-26—**State of the Art in Neurosciences.** Federation of Western Societies of Neurological Science at Silverado Country Club, Napa. Thursday-Sunday. 18 hrs. Contact: FWSNS, 525 Hurlingham Ave., San Mateo 94402. (415) 340-9084.

March 2—**10th Annual Diabetes Program.** UCD at Sacramento Inn, Sacramento. Friday.

March 7-10—**Office Endocrinology.** UCSF at Hyatt Lake Tahoe. Wednesday-Saturday. 15 hrs. $225.

March 8-10—**1984 International Symposium on Viral Hepatitis.** UCSF at Hilton, San Francisco. Thursday-Saturday.

March 8-10—**Advanced Nephrology and Hypertension: Nephrology for the Consultant.** Annenberg Center for Health Sciences and UCSD at Annenberg Center, Rancho Mirage. Thursday-Saturday. 18 hrs. Contact: Annenberg Center for Health Sciences, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 340-3911, ext. 1661.

March 14—**Arthritis of the Single Joint.** LLU. Wednesday. $50.

March 15-16—**New Concepts in Hemophilia.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Friday.

March 15-17—**4th International Conference in Coccidioidomycosis.** American College of Chest Physicians at Hyatt Islandia Hotel, San Diego. Thursday-Friday. Contact: AACP, Div. of Ed., 911 Busse Hwy, Park Ridge, IL 60068.

March 15-17—**Frontiers in Rheumatology.** Annenberg Center for Health Sciences of the Eisenhower Medical Center, Rancho Mirage. Thursday-Saturday. 16 hrs. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

March 26-27—**Circulatory Problems in the Aging Adult.** Eisenhower Medical Center at Annenberg Center, Rancho Mirage. Monday-Tuesday. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 621-7322.

March 29-30—**1984 Updates: Medical and Behavioral Treatment.** See Of Interest To All Physicians, March 29-30.

March 31-April 7—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Hotel, Mauna Kea, HI. One week.

April 4—**Thyroid '84.** The Hospital of the Good Samaritan at Hyatt Regency Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, Coordinator of Symposia, 616 S. Witmer St., Los Angeles 90017. (213) 977-2352.

April 12-14—**Surgery of the Upper Extremity in Rheumatoid Arthritis.** Eisenhower Medical Center at Annenberg Center, Rancho Mirage. Thursday-Saturday. 12 hrs. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

April 28-May 5—**New Concepts in Gastroenterology: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Poplin Creek Estate, Ojai. One week. 24 hrs. Contact: Richard F. Paris, MD. (208) 788-4995.

May 7-11—**Advances in Internal Medicine.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

May 7-11—**Clinical Microbiology Update.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 29.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-1336, ext. 129.

OBSTETRICS AND GYNECOLOGY

January 25-27—**Basic Obstetric Ultrasound.** American College of Obstetrics and Gynecology at Sheraton Plaza Hotel, Palm Springs. Wednesday-Friday. 16 hrs. Contact: ACOG Registrar, Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

February 4-10—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui. One week. 23 hrs. $450.

February 5-9—**Ob/Gyn Update: 1984.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday.

February 11-12—**Los Angeles Ob/Gyn Forum.** Los Angeles Ob/Gyn Society at Beverly Hilton Hotel, Beverly Hills. Sat-

(Continued on Page 136)

The time is near for California Medical Association's 113th Annual Session

February 10-15, 1984

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It's just around the corner...

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Watch for these exciting programs!

Schedule-at-a-glance

THURSDAY AND FRIDAY, February 9 & 10

CPR—Advanced Cardiac Life Support Workshop—Provider Course, $195

FRIDAY, February 10

8:00 am Flexible Sigmoidoscopy/Colorectal Cancer Screening Workshop, $75

8:30 am Techniques and Problems in Handling Mass Casualties, $25

9:00 am I'm Concerned About a Colleague's Practice—What Do I Do? $25

Prevention of Prescription Drug Abuse, $35

Exhibits open until 5:00 pm

11:00 am CPR—Advanced Cardiac Life Support Workshop—Recertification Course, $100

2:00 pm Anorexia Nervosa, Bulimia, Obesity: Psychology, Diagnosis and Treatment

SATURDAY, February 11

8:00 am Acquired Immune Deficiency Syndrome (AIDS)—The Epidemiology, Diagnosis, Etiology and Treatment

Infections of the Central Nervous System

Hazards of Everyday Living, $5

8:15 am Recent Advances in Occupational Diseases—1984, $10

8:30 am CPR—Basic Cardiac Life Support, $25

Diagnostic Problems in Pediatric Allergy, $20

Coma: Medical, Ethical and Legal Issues—Dilemmas in Caring for the Severely Brain Damaged Patient

Update on Laser Therapy in Ophthalmology, $30

Otolaryngology for the Primary Care Physician

Medical Student Well-Being: A Preventive Approach to Physician Impairment

9:00 am Why Cosmetic Surgery of your Patient?

Early Markers of Chemical Dependence, $10

CMA House of Delegates

Exhibits open until 5:00 pm

12:30 pm Matching: A Workshop on Residency Programs and Career Planning

1:00 pm Recent Advances in Surgical Diagnosis

Skin Cancer: Everyone's Problem

Environmental Toxicology for the Clinician, $5

1:30 pm CPR—Basic Cardiac Life Support, $25

New Concepts in Otolaryngology/Head and Neck Surgery

5:00 pm Aerobics Hour

7:30 pm Saturday Night Jazz

February 10-15, 1984 • Disneyland Hotel, Anaheim

All events are free unless otherwise noted

SUNDAY, February 12

8:00 am Diagnostic Imaging of the Chest: How, When and Why to Use It, $20
Update 1984—Premature Labor, Premature Delivery, the Premature Infant—Care, Ethical and Legal Considerations
Sprains, Strains and Simple Fractures
Geriatric Rehabilitation
Suture Course, $60
Computers in Medicine, $20 am, $15 pm
8:15 am Selected Topics in Family Practice
8:20 am Update of Selected Topics in Internal Medicine
8:30 am Blood Transfusions
New Concepts in Emergency Care, $18
Anticipatory Guidance During Childhood and Adolescence—A Primer
Immunization Update, $5
Office Urology for Primary Care Physicians
9:00 am Exhibits open until 5:00 pm
Family Day at Disneyland until 9:00 pm, $8
11:30 am KEYNOTE SPEAKER NORMAN SHUMWAY Heart and Heart-Lung Transplantation: The Stanford Experience
1:00 pm The Practicing Physician: Coping With Stress, $25
Ambulatory Surgical Centers
1:30 pm The Medical Gender Gap: Fact or Fiction?
Venereal Disease Update
2:00 pm Difficult Decisions: Prevention of Mental Retardation and Other Developmental Disabilities
4:00 pm CMA House of Delegates
6:30 pm CMA and CMA Auxiliary Presidents' Reception
7:30 pm CMA and CMA Auxiliary Presidents' Dinner Dance, $40 per person

MONDAY, February 13

1:30 pm CMA House of Delegates

TUESDAY, February 14

1:30 pm CMA House of Delegates

WEDNESDAY, February 15

9:00 am CMA House of Delegates

Pick up a complete schedule at the Advance Registration Desk or the Registration Desk at the Disneyland Hotel. Registration hours are Thursday, February 9 from 1:00-5:00 pm; Friday, February 10 through Tuesday, February 14 from 7:30 am-5:00 pm; and Wednesday, February 15 from 7:30 am-noon.

(Continued from Page 132)

urday-Sunday. 10 hrs. $80. Contact: Director of Medical Education, LA Ob/Gyn Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 13-17—**39th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Director of Medical Education, Ob/Gyn Assembly of S. California, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 15-17—**Common Problems in Obstetrics.** American College of Obstetrics and Gynecology at Riviera Hotel, Las Vegas. Wednesday-Friday. 16 hrs. Contact: ACOG Registrar, Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

February 16-18—**Advanced Fetal Heart Rate Monitoring.** Memorial Hospital Medical Center and UCI at Sheraton-Waikiki, Oahu. Thursday-Saturday. 10 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801-1428.

February 18—**Endometriosis Update: 1984.** Scripps Clinic and Research Foundation, La Jolla. Saturday. Contact: Dianne Tisue: Conf. Coord., Scripps Clinic and Research Fndn, 10666 N. Torrey Pines Rd., La Jolla 92037.

February 25—**Office Gynecology.** UCLA. Saturday.

March 14-17—**Contemporary Obstetrics: A Guide to the Physician in Practice.** March of Dimes Birth Defects Foundation, Orange County Chapter, UCI and St. Joseph Hospital at Disneyland Hotel, Anaheim. Wednesday-Saturday. 21.5 hrs. $210. Contact: Michelle S. Wampler, March of Dimes Birth Defects Foundation, Orange County Chapter, Rea Community Center, 661 Hamilton, #650, Costa Mesa 92627-2690.

March 23-25—**Gynecologic Surgery with Emphasis on Gynecologic Urology.** Memorial Hospital Medical Center and UCI at Hilton Riviera, Palm Springs. Friday-Sunday. 15 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

May 5-10—**32nd Annual Clinical Meeting of American College of Obstetrics and Gynecology** at San Francisco. Saturday-Thursday. 17 hrs. Contact: ACOG, Registrar, Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

May 13-16—**Recent Advances in Obstretrics and Gynecology.** UCSD. Sunday-Wednesday.

May 30-June 2—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center and UCI at Silverado Country Club and Resort, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

OPHTHALMOLOGY

January 22-25—**53rd Mid-Winter Conference in Ophthalmology.** Research Study Club at Hilton Hotel, Los Angeles. Sunday-Wednesday. Contact: Research Study Club, P.O. Box 49412, Los Angeles 90049.

January 28—**Update on Strabismus and Pediatric Ophthalmology.** Jules Stein Eye Institute, Los Angeles. Saturday. $85. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

February 4—**Ophthalmology Residents and Fellows Day.** Jules Stein Eye Institute, Los Angeles. Saturday. 6 hrs. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

February 5-9—**Lake Tahoe Winter Vitreo-retinal Symposium.** UCD at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday.

March 1-2—**Annual Postgraduate Seminar—Retina and Choroid: Vascular, Inflammatory and Degenerative Disease.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. $375. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Med., Center for Health Sciences, Los Angeles 90024.

March 31—**Modern Ophthalmologic Procedures: ERG, VER, Ultrasonography, Tonography, Eye Movement Analysis, and Octopus Quantitative Perimetry.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $85. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

April 14—**Drug Therapy and Pharmacology Review for Ophthalmologists.** Jules Stein Eye Institute, Los Angeles. Saturday. $85. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

May 12—**Contact Lens Practice in the Mid-80's.** Jules Stein Eye Institute, Los Angeles. Saturday. $100. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

PEDIATRICS

January 21—**An Update on Pediatric Intensive Care 1984.** Valley Children's Hospital at Torino's, Fresno. Saturday. 7 hrs. $55. Contact: Jan Kidwell, RN, Outreach Education Dept., 3151 N. Millbrook, Fresno 93703. (209) 225-3000, ext. 1402.

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. One week. 21 hrs. $335.

January 27-29—**22nd Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 27-29.

January 29-February 1—**9th Annual Winter Ski and Study Symposium.** American Academy of Pediatrics, Cal. Chapters 1 and 2 at Caesars Tahoe Hotel, Lake Tahoe. Sunday-Wednesday. 10 hrs. Contact: AAP, Chapt. 2, P.O. Box 2134, Inglewood 90305.

March 11-17—**Forefronts in Pediatrics: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine sailing at Maui, Molokai, and Lania, HI. One week. Contact: Richard F. Paris, MD. (208) 788-4995.

March 15-18—**Combined Southern California Pediatric Postgraduate Meeting.** American Academy of Pediatrics, California Chapter 2 at Palm Springs. Thursday-Sunday. Contact: Eve Black, Exec. Sec., P.O. Box 2134, Inglewood 90305. (213) 757-1198.

March 24-25—**Avoiding the Pitfalls of Pediatric Office Orthopaedics.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Saturday-Sunday. 12.5 hrs. $195.

April 6-7—**Annual Pediatrics Program.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday.

April 25-27—**9th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center and UCI at Hyatt Regency, Long Beach. Wednesday-Sunday. 17 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

April 26-28—**Advances in Pediatrics.** UCSF at Mark Hopkins, San Francisco. Thursday-Saturday.

April 27-29—**Pediatric Infectious Disease.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Friday-Sunday. Contact: AAP, Div. of Cont. Ed., P.O. Box 1034, Evanston, IL 60204.

May 7-11—**The 1984 14th Annual Review of Pediatrics.** USC and Children's Hospital of Los Angeles at Los Angeles. Monday-Friday. 26 hrs. $350. Contact: USC.

May 16—**Los Angeles Pediatric Society Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

(Continued on Page 138)

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(Continued from Page 136)

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** See Psychiatry, May 17-18.

PSYCHIATRY

January 16-19—**Family Crises: Intervention Strategies.** Mental Research Institute. Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 21—**Developing a Personal Evolving Model of Therapy: What to Do After the Music of Formal Training Stops.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 22-26—**Mental Research Institute Winter Seminar** at Mental Research Institute, Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 25-29—**Intensive Review of Psychiatry and Neurology.** USC at The Palm Springs Racquet Club, Palm Springs. Wednesday-Sunday.

January 28—**Treating Depression in a Marital Context.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $60. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 29-February 3—**10th Annual Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 6-10—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 11—**The Interactional Treatment of Eating Disorders.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $95. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 11-12—**Psychoanalysis and Femininity.** San Diego Psychoanalytic Society and Institute at Vacation Village, San Diego. Saturday-Sunday. 12 hrs. $150. Contact: Esther Burstein, PhD, 1020 Prospect, La Jolla 92037. (619) 454-9374.

February 17-18—**Family Therapy and Supervision: Creating Contacts of Competence.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 25—**Issues in Interactional Theory and Research.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 9-11—**Progress in Treatment of Affective Disorders.** Central California Psychiatry Society at Rio Bravo Resort, Bakersfield. Friday-Sunday. 8 hrs. $100. Contact: Kern County Psychiatric Society, 1901 Truxton Ave., Bakersfield 93301. (805) 327-2021.

March 14-18—**The Development of the Able Mind Revisited.** Southern California Neuropsychiatric Institute at La Quinta Hotel Golf and Tennis Resort, La Quinta. Wednesday-Sunday. 24 hrs. Contact: Gail Waldron, MD, Program Director, SCNI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

March 15-17—**Mid-Life Issues: Stress, Anxiety and Depression.** John A. Burns School of Medicine, University of Hawaii at Hotel InterContinental, Maui. Thursday-Saturday. 13.5 hrs. $200. Contact: Mrs. Dee Chang, CME, Educational Specialist, 1960 East-West Rd., Honolulu, HI 96822. (808) 947-8573.

March 15-18—**Hawaiian Psychiatric Symposium.** Continuing Medical Education, Inc. at Sheraton-Waikiki. Thursday-Saturday. 25 hrs. $295. Contact: CME, Inc., 2030 E 4th St., Santa Ana 92705. (714) 547-5186.

March 29-30—**1984 Updates: Medical and Behavioral Treatment.** See Of Interest To All Physicians, March 29-30.

April 28-29—**The Cutting Edge—1984: The Psychotherapy of Borderline and Narcissistic Disorders.** UCSD at Hotel del Coronado, San Diego. Saturday-Sunday. 13 hrs. $250.

May 3-6—**28th Annual Meeting of the American Academy of Psychoanalysis** at Hyatt Regency Hotel, Los Angeles. Thursday-Sunday. Contact: AAP, 30 E. 40th St., Ste. 608, New York, NY 10016. (212) 697-4105.

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** UCD at Holiday Inn Holidome, Sacramento. Thursday-Friday.

RADIOLOGY AND PATHOLOGY

January 16-19—**Chest Radiology 1984.** UCSD. Monday-Thursday. 24 hrs. $350.

January 23-27—**Tumorous Conditions of the Bones and Soft Tissues.** American Society of Clinical Pathologists at Town and Country Hotel, San Diego. Monday-Friday. 38.5 hrs. $650. Contact: ASCP, Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

January 25-27—**Basic Obstetric Ultrasound.** See Obstetrics and Gynecology, January 25-27.

January 29-February 3—**6th Annual Winter Conference in the High Sierras.** American College of Medical Imaging at Sahara Tahoe Hotel, Lake Tahoe. Saturday-Thursday. 25 hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

February 1-3—**11th Annual Course in Genitourinary Pathology.** UCI and Memorial Medical Center of Long Beach, Long Beach. Wednesday-Friday. 24 hrs.

February 29-March 2—**4th Annual Current Approaches to Radiation Oncology, Biology, and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Sunday.

March 3-8—**National Meeting of the American Society of Clinical Pathologists and College of American Pathologists** at Las Vegas. Saturday-Thursday. Contact: ASCP, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-4855.

March 7-9—**5th Annual Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation and the Northern California Radiological Society at Granlibakken Ski and Racquet Resort, Tahoe City. Wednesday-Friday. 18 hrs. $300. Contact: Arthur B. Dublin, MD, Program Dir., SRREF, P.O. Box 19184, Sacramento 95819.

March 12-16—**International Academy of Pathology Annual Meeting.** United States-Canadian Division of the International Academy of Pathology at San Francisco Hilton. Monday-Friday. Contact: Dr. Nathan Kaufman, Sec.-Treas., USCDIAP, 1003 Chafee Ave., Augusta, GA 30904. (404) 724-2973.

March 12-16—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $400.

March 19-21—**New Imaging Technologies.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Monday-Wednesday. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

March 24—**A One-Day Seminar on CT and NMR Imaging of the Spine.** Los Angeles Radiology Society at Westin Bonaventure, Los Angeles. Saturday. 6 hrs. Contact: Richard A. Oas, MD, CT Spine, c/o LARS, 5200 Century Blvd., Ste. 920, Los Angeles 90045.

April 15-20—**Residents' Pre-Board Radiology Course.** UCSD. Sunday-Friday.

April 23-27—**Review in Immunohematology and Blood Banking.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 31.5 hrs. Contact: Regional Education-

al Activities, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-1336, ext. 129.

April 29-May 4—**4th Annual Residents' Radiology Review Course.** UCSD. Sunday-Friday. 37 hrs. $360.

May 7-11—**San Diego Imaging Symposium.** UCSD. Monday-Friday. 27 hrs. $400.

May 22-25—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Tuesday-Friday. 26 hrs. Contact: R. S. Pakusch, MD, Program Chairman. (415) 561-3764.

SPORTS MEDICINE

February 12-17—**Sports Medicine.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

March 12-16—**University of Hawaii Sports Medicine Course** at Princess Kaiulani Hotel, Waikiki, Honolulu, HI. Monday-Friday. $280. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu, HI 96822. (808) 948-8244.

May 2-6—**Mountain Medicine: 1984.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Tuesday.

May 23-26—**American College of Sports Medicine Meeting** at Town and Country Hotel, San Diego. Monday-Thursday. Contact: T. Miller, Exec. Dir., ACSM, 1440 Monroe St., Madison, WI 53706.

SURGERY

January 16-20—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

January 18-21—**17th Otological Surgery Course.** USC and St. Vincent Medical Center at House Ear Institute, Los Angeles. Wednesday-Saturday. 32 hrs. $400. Contact: James L. Sheehy, MD, HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 20-21—**6th Annual Postgraduate Course in Surgery.** UCD at Capital Plaza Holiday Inn, Sacramento. Friday-Saturday.

January 23-26—**Postgraduate Assembly in Surgery.** UCSD at Sheraton Harbor Island Hotel, San Diego. Monday-Thursday. 28 hrs.

January 25-27—**13th Annual Sierra Traumatological Society Meeting** at Granlibakken Resort, North Lake Tahoe. Wednesday-Friday. 6 hrs. $75. Contact: STS, P.O. Box 230, Stockton 95201. (209) 466-9535.

January 26-29—**Aesthetic Body Sculpture.** Plastic Surgery Educational Foundation and American Society for Aesthetic Plastic Surgery at Hotel Del Coronado, San Diego. Thursday-Sunday. 18 hrs. Contact: PSEF, Exec. Office, 233 N. Michigan Ave., Chicago, IL 60601.

January 28—**The Grand Design.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Saturday. 2 hrs. Contact: Heart Institute of the Desert, Wright Bldg., Ste. 406, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

January 28-February 4—**Temporal Bone Surgical Dissection—1984.** House Ear Institute, Los Angeles. One week. 62 hrs. $850. Contact: Antonio de la Cruz, MD, Director of Education, HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

February 2-3—**2nd Annual Symposium on Surgical Treatment of Obesity.** Dominguez Valley Hospital and King Drew Medical Center at Airport Park Hotel, Los Angeles. Thursday-Friday. 16 hrs. Contact: M. Fobi, MD, FACS. (213) 603-0116.

February 6-7—**Lasar Endoscopy Conference.** American College of Chest Physicians, Cal. Chapter at Harvey's Inn, South Lake Tahoe. Monday-Tuesday. 9 hrs. $200. Contact: Lowell Renz, MD, Room Reservations, 128 Stateline, NV 89449. (916) 739-8837.

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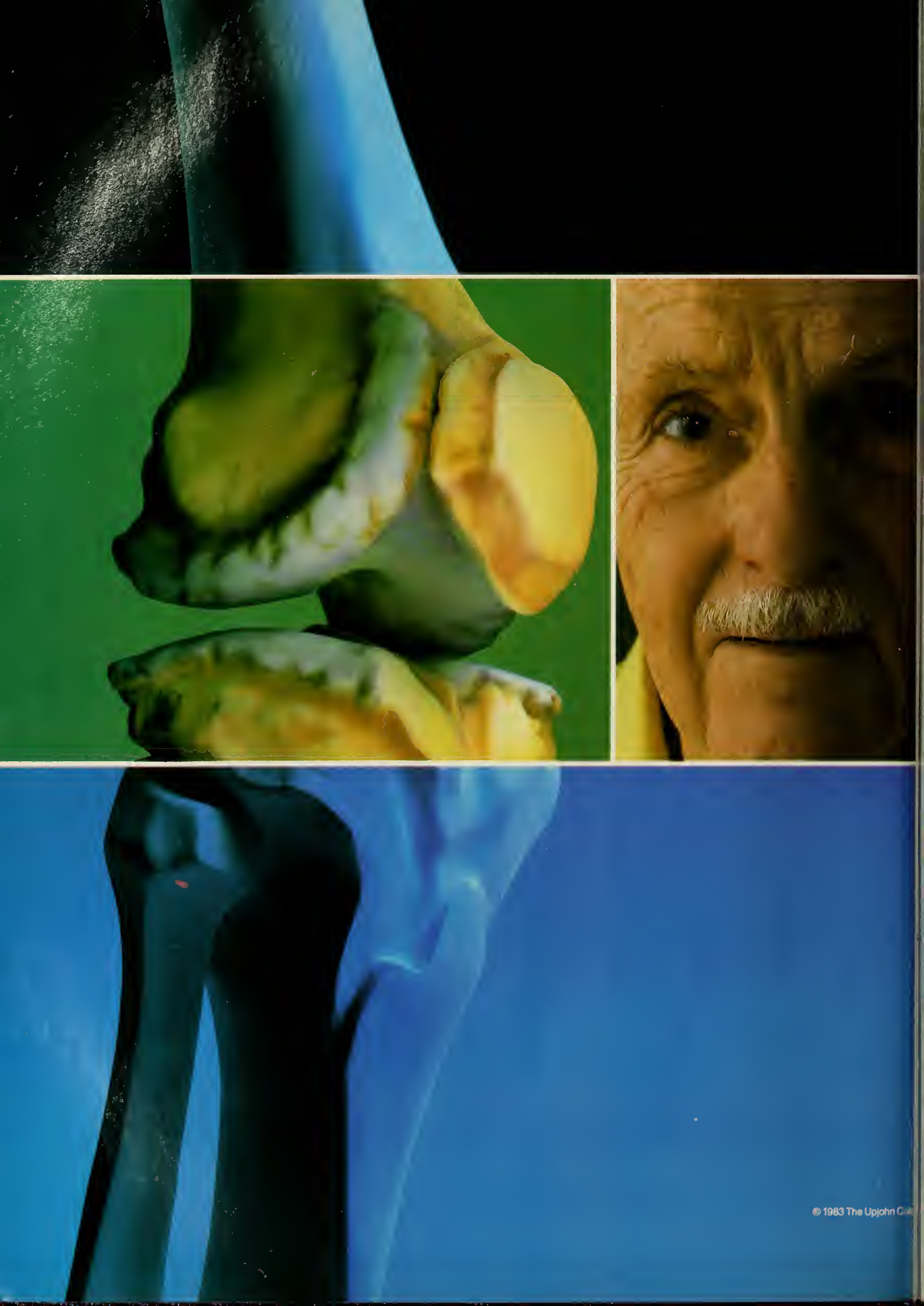

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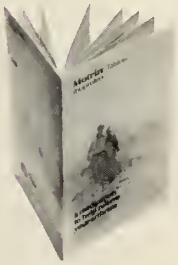

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Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

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Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

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Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

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Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship*

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown*

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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(Continued from Page 140)

February 13-18—**UCI Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

February 18-22—**The Doctor's Dilemma: The Delicate Balance Between Humanity and Technology.** Human Dimensions In Medical Education at La Jolla. Saturday-Wednesday. 32 hrs. $400. Contact: Ms. Orienne Strode, Director, HDME, 1125 Torrey Pines Rd., La Jolla 92037. (619) 459-3861.

February 19-22—**4th Annual Conference on Alcoholism and Chemical Dependency Problem Sharing/Solving in Chemical Dependency.** Annenberg Center for Health Sciences of the Eisenhower Medical Center, Rancho Mirage. Sunday-Wednesday. Contact: Annenberg Center for Health Sciences —A, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

February 23-24—**American College of Physicians 1984 Regional Meeting** at Ala Moana Hotel, Honolulu, HI. Thursday-Friday. Contact: Robert A. Nordyke, FACP, 2013 Kakela Dr., Honolulu, HI 96822.

March 2-3—**American College of Physicians 1984 Regional Meeting** at Holiday Inn, Napa. Friday-Saturday. Contact: Jerry P. Lewis, FACP, 618 Francisco Place, Davis 95616.

March 7-9—**34th Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Continuing Ed., Mt. Zion Hospital, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

March 14-17—**Contemporary Obstetrics: A Guide to the Physician in Practice.** See Obstetrics and Gynecology, March 14-17.

March 16-18—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel del Coronado, Coronado. Friday-Sunday. 20 hrs. $250. Contact: Jackie Shiller, Continuing Medical Education Associates, P.O. Box 84296, San Diego 92138. (619) 223-2997.

March 22-24—**Postgraduate Institute.** California Medical Association at Yosemite. Thursday-Saturday.

March 24—**Alcoholism: 1984.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

March 25-28—**Nutrition Conference.** UCSF at Yosemite. Sunday-Wednesday.

March 26-30—**Family Medicine Board Review Course.** UCSD at Palm Springs. Monday-Friday.

March 29-30—**1984 Updates: Medical and Behavioral Treatment.** Scripps Clinic and Research Foundation, La Jolla. Thursday-Friday. Contact: Dianne Tisue, Conference Coordinator, Scripps Clinic and Research Fndn, 10666 N. Torrey Rd., La Jolla 92037. (714) 455-9100.

April 1-4—**Dermatology for the Clinician.** UCD at Yosemite. Sunday-Wednesday.

April 6—**Laboratory Aids in Clinical Diagnosis.** LLU at Casa Royale Motor Inn, Bakersfield. Friday. 6 hrs. $75.

April 6-8—**Sexual Issues in Medical Practice.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. 14 hrs.

May 5-12—**Challenges in Acute Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Poplin Creek Estate, Ojai. One week. Contact: Richard F. Paris, MD. (208) 788-4995.

May 14-18—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

May 19-20—**12th Annual Family Practice Symposium.** Southern California Permanente Medical Group at Sheraton Universal Hotel, North Hollywood. Saturday-Sunday. 11 hrs. Contact: SCPMG, Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

May 20-24—**Family Practice Refresher Course.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Thursday.

(Continued on Page 150)

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FACULTY POSITION in community-based Family Practice Residency affiliated with the University of Washington. Seeking a Board certified, Family Practice Residency graduate for position available July 1, 1984. Duties include: curriculum planning, administration and evaluation; resident precepting; direct patient care and sharing call with the other faculty. Prefer prior teaching experience in a Family Practice Residency. Generous fringe benefits; salary based on experience. Send inquiries and CV to: Kenneth E. Gudgel, MD, Director, Family Medicine Spokane, S. 511 Pine St., Spokane, WA 99202.

ALASKA: FAMILY PRACTITIONER, Board eligible/certified, to join the Fairbanks office of Alaska's largest multi-specialty clinic. Generous guaranteed salary, benefits, and relocation allowance. Partnership opportunity. Contact: Administrator, Fairbanks Clinic, 1867 Airport Way, Fairbanks, AK 99701.

GENERAL SURGEON—Opening in multi-specialty clinic. Guaranteed salary first year plus incentive. Full fringe benefits. New hospital, and four season recreation. Contact the Budge Clinic, 225 East 4th North, Logan, UT 84321. Telephone (801) 752-0422.

ED PHYSICIAN, TACOMA, WASHINGTON: Experienced (3 yr. plus) or Boarded ED Physicians needed for locum tenens positions (2) to begin May 1 to June 1, 1984, and to continue for 4-6 months. Established group with two hospitals. Possibility of continuation if mutually agreeable. Reply with CV to: Mike Doman, MD, 1700 36th Ave., Seattle, WA 98122; (206) 323-4914 (home) or (206) 597-7600 (work).

PHYSICIAN for busy full-time Occupational Medicine—Ambulatory care position. Experience in complete medicine and minor surgery preferred. Excellent opportunity with competitive salary, malpractice paid and benefits package. Send CV to California Physicians Management Group, P.O. Box 52-B, Newport Beach, CA 92660; (714) 650-4156.

EMERGENCY PHYSICIAN—Full time position available immediately; Northern California Coastal Community, to work in a group of 5 physicians. Rural hospital base station with good mix of trauma, medicine and pediatrics. Approximately 12,000 patient visits per year. Partnership in two years. Excellent recreational facilities. Must relocate. Send CV to: Dr. Elliot Nipomnick, Seaside Hospital, 100 A St., Crescent City, CA 95531 or call (707) 458-3533.

WANTED: Residency trained, young family practitioner for busy, 3-physician Family Practice covering 600 sq. miles in beautiful northern California foothills. All aspects of general medicine; active hospital program, surgery, full obstetrics. Salary negotiable. Benefits liberal. Contact: John B. Rose, MD, P.O. Box 609, Brownsville, CA 95919; (916) 675-2457.

OB/GYN PHYSICIAN needed to join two other OB/GYN Physicians in a 39-man multi-specialty group located in San Luis Obispo, California. Board certified or eligible; California license. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Reply: Mr D. R. Molesworth, Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

OSTEOPATHIC EMERGENCY ROOM PHYSICIAN needed at the sunny eastern edge of Washington's Cascades. Flexible schedule. Contact Shane Roberts, Administrator, or Greg Maddex, D.O. at (509) 453-6561, New Valley Osteopathic Hospital, 3003 Tieton Drive, Yakima, Washington 98902.

WANTED: BOARD CERTIFIED RADIOLOGIST for large out-patient multi-specialty Clinic—Central Coast of Calif. Must have particular competence in Nuclear Medicine and Ultrasound. Salary negotiable; excellent benefits. Respond to: Box 6400, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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THE KING COUNTY JAIL is currently recruiting for a **Board eligible or certified Psychiatrist.** Experience in forensic psychiatry and/or treating chronic, recidivistic populations is helpful. Practice involves assessment, triage, medication evaluation and treatment of a large psychiatric population in a busy, metropolitan jail. A treatment team approach is utilized with a staff of psychiatrists, psychiatric nurses, and social workers. A minimum of 15 hours per week is required under contractual arrangements or through half-time salaried positions. Must be licensed in the State of Washington. For more information contact: Bruce Miyahara, Administrator, Jail Health Services, c/o Seattle-King County Dept. of Public Health, 4400 Yesler Building, 7th Floor, Seattle, WA 98104; (206) 587-2764.

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(Continued on Page 148)

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GROWING FAMILY PLANNING AGENCY seeks Gynecologist (BC/BQ)—Arizona license to supervise abortion clinic services and perform first trimester procedures. Other responsibilities will include assisting Medical Director in management of contraceptive services provided at 9 sites. 30 hours per week with opportunity for full-time within one year. Salary plus benefits, negotiable. Medical liability insurance provided. EEO/AA Employer. Send CV to: Medical Department, Planned Parenthood of Central and Northern Arizona, 1301 Sth. 7th Avenue, Phoenix, AZ 85007.

CALIFORNIA, WASHINGTON STATE: Physicians interested in developing a practice yet who value free time are wanted for an extended hour ambulatory care clinic. Salary competitive; no night call; new facility; well trained staff; unparalleled major city location. Applicants should be Board qualified in IM/FP/ER. Please send CV to Michael Goluska, MD, CHEC Medical Centers, 2200 6th Ave, #1200-G, Seattle, WA 98121, (206) 624-6888.

WANTED: PHYSICIANS for new Emergency Clinics in Western Washington. Attractive locations. Excellent growth opportunity. Excellent salary. Bonus incentives, equity positions. Malpractice paid, educational benefits. Should be Board eligible in EM/FP/IM with experience in active patient care. Send CV to Box 6406, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

SAN FRANCISCO BAY AREA—50 MD multi-specialty private group practice established 25 years ago, seeking a well-qualified OBSTETRICIAN GYNECOLOGIST to join our busy 4-physician department in their general OB/GYN work. Excellent location in the Santa Clara Valley, 45 minutes from San Francisco, 10 minutes from Stanford University. Send CV to: Recruitment Committee, P.O. Box 3496, Sunnyvale, CA 94088-3496.

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FAMILY MEDICINE FACULTY POSITIONS. Due to expansion, the Department of Family Practice at the San Bernardino County Medical Center is recruiting for immediate vacancies, as well as vacancies for July 1984. This academic department of 17 faculty members is seeking Board certified Family Physicians with prior teaching experience in Family Medicine. Demonstrated research activities are desired. Send inquiries and curriculum vitae to: Merrill N. Werblun, MD, Chairman, Department of Family Practice, P.O. Box 3571, San Bernardino, CA 92413.

GYNECOLOGY ASSISTANT STAFF POSITION. OB/GYN: Resident level opportunity for 2 physicians to assist 5 full-time obstetricians and gynecologists in hospital based multispeciality practice. Major teaching and research facility affiliated with the University of Washington. Please contact: A. Solola, Chief, OB/GYN, Pacific Medical Center, 1200 12th Ave S, Seattle, WA 98144; (206) 326-4180.

OPPORTUNITY. Looking for preventively oriented physician to work with dentist and other professionals dealing with patients with TMJ and other related health problems. Lease space available in new professional office building, 1,777 sq. ft. on ground floor (divisible), 4,420 sq. ft. on second floor (divisible). Close to area hospitals and growing community. Reply to Robert T. Parigian, DDS, Inc., 4000 N. Wheeler Ave, Suite 1, La Verne, CA 91750; (714) 596-6555.

WASHINGTON STATE! Allergist and OB/GYN wanted to join multi-specialty clinic in scenic, fast-growing area near Seattle. Excellent practice opportunity in ideal setting Please call or write North Kitsap Medical Center, 20700 Bond Road NE, Poulsbo, WA 98370; (206) 779-5521.

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MINOR EMERGENCY CENTERS: Washington-South Puget Sound Area—Full-time/some part-time positions available. Reply with CV to Terry Kendrick, MD, 6655 Kimball Drive, Gig Harbor, WA 98335 or call 1-(206)-851-8182.

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RADIOLOGIST—Solo practice in new hospital located in Central New Mexico. Ideal family living in prosperous community of 11,000, with easy access to mountain recreation areas. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1-(800)-545-4030, extension 3050.

EMERGENCY/FAMILY PRACTICE position available—Wheeler Hospital's Emergency/Outpatient Service, Gilroy, California. 20,000 patient visits per year. Good specialty backup coverage. Pleasant community, good schools, churches, recreation. Fifty minutes to Monterey, ninety minutes to San Francisco. Contact T. Scott Laird, MD, Director, Emergency Service, 651 W. Sixth St, Gilroy, CA 95020; (408) 842-5621.

SEATTLE, WASHINGTON: Emergency Medicine Faculty. Full-time attending position at University Hospital Emergency Medicine Service, University of Washington. Responsible for patient care, housestaff and student teaching, clinical research. Board certified or eligible in IM, EM, Surg or FM. Inquiries to: Mickey Eisenberg, MD, University Hospital RC-02, 1959 NE Pacific St, Seattle, WA 98195.

GENERAL SURGEON NEEDED—Multispecialty Group. Excellent opportunity for qualified individual. Contact: Dr Robert Caplan, 1-(303)-776-1234, 1925 Mountain View, Longmont, CO 80501.

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(Continued on Page 156)

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(Continued from Page 144)

May 29-June 2—**11th Annual UCLA Santa Monica Hospital Medical Center Family Practice Refresher Program.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Tuesday-Saturday. 35.5 hrs. $385.

IDAHO

January 28-February 4—**Far Western Medical Association—Winter Scientific Meeting—What's New in Medicine?** Sun Valley. One week. Contact: FWMA, P.O. Box 3817, Van Nuys, CA 91407.

February 18-25—**Up-to-Date Cardiac Therapy: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Sun Valley. 24 hrs. Contact: Richard F. Paris, MD, (208) 788-4995.

February 19-25—**Effective Management of Common Sports Injuries: An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

February 25-March 3—**Effective Diagnosis and Treatment of Infectious Diseases—An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

February 26-March 3—**Current Therapy for Dermatological Disease: An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

March 4-10—**New Considerations in Family Practice: A Review.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

March 25-April 1—**Procedures and Concepts in Ambulatory Gynecology: An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

April 1-7—**Establishing Precise Radiographic Diagnoses for Traumatic Injuries.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

MONTANA

March 22-24—**Big Sky Lung Summit.** American Lung Assn. of Montana at Big Sky of Montana "Ski the Sky." Thursday-Saturday. Contact: ALA of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 153)

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY

PROCARDIA* (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well toleraed, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

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*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*

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RU-TUSS® II
sustained release capsules

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DESCRIPTION: Each sustained release capsule contains 12 mg of Chlorpheniramine Maleate, USP and 75 mg of Phenylpropanolamine Hydrochloride, USP in a base to provide prolonged activity.
INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).
CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis. Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.
WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.
Usage in pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.
PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal function impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, Alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.
ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with Chlorpheniramine Maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis histeria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.
DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.
OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.
HOW SUPPLIED: Green and clear capsules with green and white beads. Bottles of 100 tablets. NDC 0524-0031-01
Store at controlled room temperature 15-30°C (59°-86°F.).
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(Continued from Page 150)

January 14-15—**Second Albuquerque Family Practice Seminar.** Albuquerque. Saturday-Sunday. Marriott Hotel. 13 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, P.O. Box 23070, Albuquerque 87192. (505) 298-5300.

January 17-21—**Rocky Mountain Neuro-Ophthalmology Society 10th Annual Meeting and Course.** Snowbird, Utah. Tuesday-Saturday. Snowbird Lodge. Contact: T. J. Carlow, MD, RMNOS, 302 Juniper Hill Rd., NE, Albuquerque 87122. (505) 293-2963.

February 3-5—**Advances in Internal Medicine IV.** Albuquerque. Friday-Sunday. Veterans Administration Medical Center. 15 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

February 6-10—**Alta Medical Conference: Diabetes 1984.** Monday-Friday. Alta, Utah. 10 hrs. AMA Cat. I, NM Cat. IV. Contact: Neil I. Kaminsky, MD, 717 Encino Pl., NE, Albuquerque 87102. (505) 842-6762.

February 19-22—**Annual Meeting/South Central Association of Blood Banks.** Albuquerque. Sunday-Wednesday. Albuquerque Convention Center. 28 hrs. AMA Cat. I, NM Cat. IV. Contact: Toby L. Simon, MD, P.O. Box 25445, Albuquerque 87125. (505) 843-6227.

February 23-25—**17th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

February 24-26—**12th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 11 hrs. NM Cat. IV. Contact: David Lorber, MD, 1101 Medical Arts Ave., NE, No. 4, Albuquerque 87102. (505) 842-5105.

February 27-March 2—**Purgatory Ski Symposium at Tamarron.** Tamarron, Colorado. Monday-Friday. Tamarron Lodge. 20 hrs. AAFP Prescribed. Contact: Jack Greenberg, MD, Bernalillo County Chapter, AAFP, 2121 Juan Tabo NE, Albuquerque 87112. (505) 292-4500.

March 18-21—**Rural Health Care: Bringing It Home.** Albuquerque. Sunday-Wednesday. Convention Center. 19 hrs. AMA Cat. I, NM Cat. IV. Contact: Judy Harris, RN, New Mexico Health Resources, Inc., P.O. Box 8735, Albuquerque 87198.

May 3-4—**New Mexico Medical Society Annual Meeting.** Santa Fe. Thursday-Friday. Hilton Inn. 10 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Ste 204, Albuquerque 87108. (505) 266-7868.

May 24-25—**Chronic Pain: Current Status and Future Directions.** Santa Fe. Thursday-Friday. La Fonda Hotel. 10¼ hrs. NM Cat. IV. Contact: Ms Helene Slansky, Coordinator, Santa Fe Neurological Sciences Institute, St. Vincent Hospital, Box 5764, Santa Fe 87501. (505) 983-4744.

July 16-19—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, P.O. Box 23070, Albuquerque 87192. (505) 298-5300.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contac: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

EMERGENCY MEDICINE

February 2-4—**Evaluation and Management of Medical Emergencies.** Bend. Thursday-Saturday. Inn of the Seventh Mountain-Mt. Bachelor. Contact: Veronica Story, Oregon Chap., Am. College of Emergency Physicians. (503) 226-1555.

FAMILY PRACTICE

February 13-17—**15th Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: OHSU-CME.

March 1-4—**Update in Rheumatology: Spring Ski at Mt. Bachelor.** Thursday-Sunday. Inn of the Seventh Mountain, Bend. Contact: OHSU-CME.

May 18-19—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion Motor Inn at Jantzen Beach. Contact: OHSU-CME.

SURGERY

March 2-3—**Difficult Problems in Surgery: Gastrointestinal Malignancies.** Portland. Friday-Saturday. Red Lion-Lloyd Center. Contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

February 5—**March of Dimes Symposium: "Normal or Not?"** Portland. Sunday. Red Lion at Jantzen Beach. Contact: OHSU-CME.

March 8-9—**Occupational Medicine.** Portland. Thursday-Friday. Red Lion at Jantzen Beach. Contact: OHSU-CME.

March 29-30—**Health Problems in the Workplace.** Thursday-Friday. Portland. Red Lion-Lloyd Center. Contact: OHSU-CME.

March 29-31—**First Annual Mt. Bachelor Winter Sports and Mountaineering Medicine Conference.** Bend. Sponsor: Siskiyou General Hospital, Yreka, California. Thursday-Saturday. Inn of the Seventh Mountain. 18 hrs. $195, physicians; $170, nurses and physical therapists. Contact: Daniel A. Williams, Jr, MD, 746 S. Main, Yreka, CA 96097. (916) 842-4383.

April 12-13—**School of Medicine Alumni Scientific Sessions and Sommer Lectures.** Portland. Thursday-Friday. OHSU Campus. Contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

(Continued on Page 157)

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(Continued from Page 148)

PRACTICES AVAILABLE

LOS ANGELES/SOUTH BAY—Great Emergi-center or Industrial Practice location. GP and Free-standing 4,000 sq. ft. medical building. Very busy intersection. Senior seller now grosses $250,000. This is a fantastic opportunity. Valuable real estate with terms to qualified buyer. Million dollar potential. Call or write Professional Practice Sales, 364 East First St, Tustin, CA 92680; (714) 832-0230.

PEDIATRIC PRACTICE FOR SALE in Southern California grossing over $200,000. Spacious new office in Medical center across the street from 200 bed community hospital. College town. Middle class community. Excellent coverage for nights and weekends. Write Box 6404, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

BEAUTIFUL WESTERN WASHINGTON 45 minutes from Seattle. Practice available for IM, FP, or GP. Doctor retiring. Just walk in and take over. Very generous terms but act now as this offer expires February 15. (206) 428-2626.

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SANTA ROSA FAMILY PRACTICE. Located in "the" medical village in Santa Rosa, this practice has been established for 27-years. Year ended June 1983 collected $162,500. Prior year realized $207,200 when owner devoted more attention.

NORTH COAST ORTHOPEDIC SURGERY PRACTICE. North of San Francisco, this practice realized approximately $350,000 in collections with an extremely attractive profit to owner for most recent fiscal year ended.

Professional Practice Sales, 1428 Irving Street, San Francisco, CA 94122; (415) 661-0700.

RENTON, WASHINGTON. Family Practice and equipment (for sale). Easy down, 3 year amortization. Underlying lease of large clinic available. (206) 271-7637.

SANTA ROSA, CALIFORNIA. Busy Family Practice 145K gross, good net; nice, newly equipped office. $70,000, negotiable terms. Please reply Box 6410, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

CALIFORNIA AND WESTERN STATES. HIGH INCOME practices for sale: Endocrinology, Radiology, Nephrology, Neurosurgery, Invasive and Noninvasive Cardiology, OB/GYN, Psychiatry, Internal, Family, Pediatric, Surgery, others. Mary Bradshaw, Professional Practice Opportunities, 21 Altamount Drive, Orinda, CA 94563; (415) 376-0762. Sales, Appraisals, Consulting, Placement, Résumé preparation service.

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VANCOUVER, WASHINGTON. Lease, 1,860 sq. ft. 3 doctor suite, Medical Dental bldg. Shared reception room. Remodeled, redecorated, spotless. Adjacent ample parking, shops, restaurants, hospital 15 blocks. Craig Angelo, 1 (206) 694-3343.

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Park City Conference

March 26-30, 1984
NUTRITION IN CONTEMPORARY MEDICINE
$225 fee, CME Credit Available

Information/Registration:
Jennifer Fossum
Division of Gastroenterology
University Medical Center
Salt Lake City, UT 84132
(801) 581-3581

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NO. CALIFORNIA 1428 Irving St., San Francisco, CA 94122 (415) 661-0700

(Continued from Page 154)

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE GRAND ROUNDS

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Wednesday—8:00-9:00 a.m. Contact: Thomas Schwenk, MD, (801) 581-8633.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo. UT 84601. (801) 373-7850 (Ext 2143).

* * * *

January 25-28—**27th Midwinter Conference on Chest Disease** (Sponsor: Intermountain Thoracic Society). Wednesday-Saturday. Snowbird. $170. Contact: Frank Brough, PhD, (801) 484-4456.

January 27-29—**8th Annual University of Utah Seminar on Sexual Function/Dysfunction.** Friday-Sunday. Yarrow/Holiday Inn, Park City. Contact: Don Strassberg, PhD, (801) 581-5809.

February 1-3—**Common Problems in Pediatrics** (Sponsor: University of Utah). Sunday-Tuesday. Salt Lake City. 13 hrs. Fee to be announced. Contact: Wendy Ellis, (801) 581-3573.

February 8-11—**Practical Neurology for Clinicians** (Sponsor: University of Utah). Wednesday-Saturday. Hotel Utah, Salt Lake City. 22 hrs. Fee to be announced. Contact: J. Richard Baringer, MD, (801) 581-8664.

February 13-16—**13th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Monday-Thursday. Salt Lake City Hilton. 28 hrs. Fee to be announced. Contact: Linda Twitchell, (801) 581-8633.

February 17-21—**29th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. 16 hrs. Fee to be announced. Contact: K. C. Wong, MD, (801) 581-6115.

February 18-22—**25th Annual OB/GYN Update** (Sponsor: University of Utah). Saturday-Wednesday. Park City, 14½ hrs. Fee to be announced. Contact: James Scott, MD, (801) 581-5501.

February 22-25—**Gynecologic Oncology Update** (Sponsor: University of Utah). Wednesday-Saturday. Park City. 14½ hrs. Fee to be announced. Contact: James Scott, MD, (801) 581-5501.

February 27-March 2—**3rd Annual Park City Dermatology Seminar** (Sponsor: University of Utah). Monday-Thursday. Park City Yarrow (Holiday Inn). 18 hrs. Fee to be announced. Contact: Gerald Krueger, MD, (801) 581-7837.

February 29-March 3—**Nuclear Medicine Update** (Sponsor: University of Utah). Wednesday-Saturday. Park City Yarrow (Holiday Inn). 23 hrs. Fee to be announced. Contact: Andrew Taylor, MD, (801) 581-2716.

March 3-10—**Primary Care: Clinical Problems in Otolaryngology—Head and Neck Surgery** (Sponsor: University of California, San Francisco). One week. Park City. Contact: UCSF, Extended Programs in Medical Education, Room 569U, San Francisco 94143. (415) 666-4251.

March 5-9—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. 25 hrs. Fee to be announced. Contact: Jennifer Fossum, (801) 581-7803.

March 8-9—**Lasers in Urologic Surgery** (Sponsor: University of Utah). Thursday-Friday. Park City Yarrow (Holiday Inn). 11 hrs. Fee to be announced. Contact: Jay Smith, MD, (801) 581-7674.

March 9-10—**Primary Care of Hand Injuries** (Sponsor: University of Utah). Friday-Saturday. Park City Yarrow (Holiday Inn). 9½ hrs. Fee to be announced. Contact: Ronald Mann, MD, (801) 581-3713.

March 12-16—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. 24 hrs. Fee to be announced. Contact: Jennifer Fossum, (801) 581-3581.

(Continued on Page 160)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fitfh West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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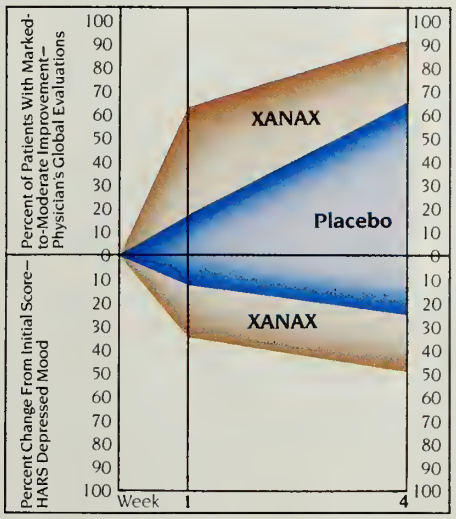
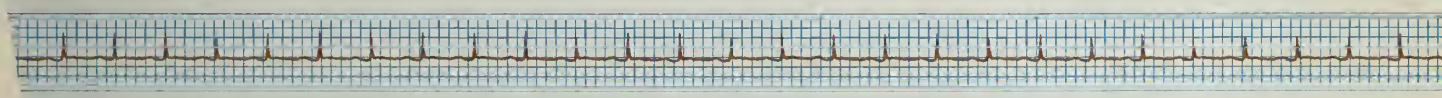
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy



- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file, The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets

alprazolam Ⓒ IV

XANAX® Tablets ©
(alprazolam)

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. BS-1

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

(Continued from Page 157)

March 12-16—**Introduction to Microcomputers for the Primary Care MD** (Sponsor: University of Utah). Monday-Friday. Park City Yarrow (Holiday Inn). 22½ hrs. Fee to be announced. Contact: Larry Lutz/Wayne Peay, (801) 581-8052.

March 16—**Annual Clinical Ophthalmology Meeting** (Sponsor: University of Utah). Friday. Salt Lake City. 6 hrs. Fee to be announced. Contact: Mano Swartz, MD, (801) 581-6384.

March 21-23—**Infection Control Update** (Sponsor: University of Utah). Wednesday-Friday. Salt Lake City. 15 hrs. Fee to be announced. Contact: Sego Matsumiya, RN, (801) 582-6384.

March 22-23—**6th Annual Conference on Medical Genetics** (Sponsor: University of Utah). Thursday-Friday. U of U campus. 14 hrs. Fee to be announced. Contact: John Carey, MD, (801) 581-8943.

March 26-30—**4th Annual Nutrition in Contemporary Medicine Conference** (Sponsor: University of Utah). Monday-Friday. Park City, Shadow Ridge Hotel. 29½ hrs. Fee to be announced. Contact: Jennifer Fossum, (801) 581-7803.

April 20—**Symposia in Infectious Disease** (Sponsor: University of Utah). Friday. Salt Lake City, Hotel Utah. Credit and fee to be announced. Contact: Zell McGee, MD, (801) 581-8201.

June 3-6—**American Society for Lasers in Medicine and Surgery** (Sponsor: University of Utah). Monday-Wednesday. Salt Lake City. 8 hrs. Fee to be announced. Contact: John Dixon, MD, (801) 581-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

January 19-21—**Washington State Academy of Ophthalmology-1984 Annual President's Meeting.** Seattle. Thursday-Saturday. Sheraton Hotel. Contact: WSAO, Patti Smith, Executive Secretary, 2033 Sixth Avenue, Suite 900, Seattle 98121. (206) 623-4801.

January 20—**Gynecologic Surgery.** Seattle. Friday. Virginia Mason Hospital Auditorium. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

January 20—**Sexual Exploitation of Children.** Seattle. Friday. Westin Hotel. Contact: U/W.

January 20—**Hypertensive Diseases in Pregnancy.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 21—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

January 25—**Ambulatory Pediatrics Management.** Seattle. Wednesday. Northwest Hospital. Contact: Charlotte Kennedy, Northwest Hospital, Education and Training Dept., 1550 N. 115th St., Seattle 98133. (206) 364-0500, ext. 1737.

January 25-26—**Welding and Painting Hazards.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

January 26-27—**Medical and Surgical Management of Heart Disease 1984.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

January 27—**Clinical Diagnosis and Therapy of Influenza.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 9—**Management of Safety and Health Programs.** Seattle. Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

February 10—**Stress and the Physician.** Seattle. Friday. Virginia Mason Hospital Auditorium. Contact: VMMC.

February 11-18—(IDAHO) **Medicine and Society in History.** Sun Valley. Saturday-Saturday. Elkhorn Club. Contact: U/W.

February 12-17—(IDAHO) **Sun Valley Primary Care Conference.** Sunday-Friday. The Lodge, Sun Valley. Contact: Marilyn Carlson, Secretary, Education and Training Department, Northwest Hospital, 1550 North 115th Street, Seattle 98133. (206) 364-0500, ext. 1737.

February 17-18—**Winter Clinical Symposium.** Wenatchee. Friday-Saturday. Thunderbird Motor Inn. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

February 18—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

February 18-25—(IDAHO) **Sports Medicine.** Sun Valley. One week. Contact: U/W.

February 23-24—**Respiratory Protection.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

February 24-25—**Revolutions in Laboratory Medicine and Pathology: What Clinicians Need to Know.** Seattle. Friday-Saturday. Virginia Mason Hospital Auditorium. Contact: VMMC.

February 29—**Laboratory Diagnosis for Clinicians.** Seattle. Wednesday. Northwest Hospital. Contact: Charlotte Kennedy, Northwest Hospital, Education and Training Dept., 1550 N. 115th St., Seattle 98133. (206) 364-0500, ext. 1737.

March 1-2—**Hospital Infections 1984.** Seattle. Thursday-Friday. Contact: U/W.

March 2—**Occupational Neurological Diseases.** Seattle. Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

March 3-10—(HAWAII) **Diagnosis and Drug Therapy.** Saturday-Saturday. Sheraton Royal Waikoloa, Island of Hawaii. Contact: U/W.

March 8—**Diabetes: Latest Concepts in Treatment.** Seattle. Thursday. Ballard Community Hospital. Contact: U/W.

March 9-10—**Hematology and Oncology.** Seattle. Friday-Saturday. Museum of History and Industry. Contact: U/W.

March 10-17—(HAWAII) **Financial Planning for Physicians.** Saturday-Saturday. Inter-Continental Hotel, Maui. Contact: U/W.

March 14—**Medical Ethics.** Seattle. Wednesday. Northwest Hospital. Contact: Charlotte Kennedy, Northwest Hospital, Education and Training Dept., 1550 N. 115th St., Seattle 98133. (206) 364-0500, ext. 1737.

March 15-18—**45th Annual Meeting of the North Pacific Society of Neurology and Psychiatry.** Seattle. Thursday-Sunday. Contact: Mary Helen Pullen, Executive Secretary, Department of Neurology, Oregon Health Sciences University, Portland, OR 97201. (503) 225-7772.

March 17—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

March 17-24—(HAWAII) **Obstetrics and Gynecology.** Saturday-Saturday. Waikiki Hyatt, Oahu. Contact: U/W.

March 18-25—(HAWAII). **The Spine.** Sunday-Sunday. Westin Wailea Beach, Maui. Contact: U/W.

March 21-23—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

March 22-23—**Advanced Cardiac Life Support.** Seattle. Thursday. U/W Health Sciences Center. Contact: U/W.

March 24—**Office Lab Diagnosis for Clinicians.** Seattle. Saturday. U/W Health Sciences Center. Contact: U/W.

March 24-31—(HAWAII) **The Injured Patient: Controversies and Challenges.** Saturday-Saturday. Kauai Sheraton, Kauai. Contact: U/W.

March 29—**Pediatric Ophthalmology.** Seattle. Thursday. Children's Orthopedic Hospital. Contact: Patti Smith, Meeting Coordinator, Washington State Academy of Ophthalmology, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

March 31-April 7—(HAWAII) **High-Risk Infants and Adolescents.** Saturday-Saturday. Inter-Continental Hotel, Maui. Contact: U/W.

April 2-15—**Rehabilitation Medicine Review.** Seattle. Monday-Sunday. Sheraton Hotel. Contact: U/W.

April 4-6—**Introduction to Industrial Hygiene.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

April 5-6—**Arrythmias.** Seattle. Thursday-Friday. U/W Health Sciences Center. Contact: U/W.

April 6—**John, Jane and Baby Doe: Bioethical Issues.** Seattle. Friday. Children's Orthopedic Hospital. Contact: U/W.

April 7—**Schizophrenia.** Seattle. Saturday. Madison Hotel. Contact: U/W.

April 12-14—**Chronic Disease in Office Practice.** Seattle. Thursday-Saturday. Seattle Sheraton. Contact: U/W.

April 14-15—**Patient Safety in Anesthesia.** Seattle. Saturday-Sunday. Westin Hotel. Contact: Patti Smith, Executive Secretary, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

April 20-21—**Endocrine Day.** Union. Friday-Saturday. Alderbrook Inn. Contact: U/W.

April 21—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

April 26—**Travel and Medicine.** Seattle. Thursday. Park Hilton Hotel. Contact: U/W.

April 27-28—**Industrial Back Pain.** Seattle. Friday-Saturday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: June 8-12, 1984, Valdez Convention Center.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 27-28, 1984, Scottsdale Conference Center, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 10-15, 1984, Disneyland Hotel, Anaheim.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: 1984—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1984—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-28, 1984, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 3-6, 1984, Desert Inn, Las Vegas.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 2-4, 1984, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Scientific Session: 1984—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 24-28, 1984, Jackson Lake Lodge, Moran.

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April 28—**Medicine and Religion.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

May 3-4—**Health Issues for Exercising Women.** Seattle. Thursday-Friday. U/W Health Sciences Center. Contact: U/W.

May 5-6—**Advanced Cardiac Life Support.** Seattle. Saturday-Sunday. U/W Health Sciences Center. Contact: U/W.

May 11—**Adverse Drug Reactions in Surgery.** Seattle. Friday. Ballard Hospital. Contact: U/W.

May 12-13—**Pharmacology for Anesthesiologists.** Seattle. Saturday-Sunday. U/W Health Sciences Center. Contact: U/W.

May 16-18—**Noise Measurement and Control.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

May 17-18—**Prevention of Chronicity in Back Pain.** Seattle. Thursday-Friday. Seattle Sheraton. Contact: U/W.

May 18—**Basic Computer Understanding.** Seattle. Friday. Seattle Trade Center. Contact: U/W.

May 19—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

May 24-25—**Hereditary Diseases of the Nervous System.** Seattle. Thursday-Friday. Mayflower Park Plaza. Contact: U/W.

June 1-2—**Health Hazards in the Modern Office.** Seattle. Friday-Saturday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

June 14-15—**Use of Microcomputers in Occupational Safety and Health.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 12-13—**Second Annual Conference on Occupational Hazards to Health Care Workers.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 27-29—**Seafair VI Pediatric Anesthesia and Intensive Care.** Seattle. Friday-Sunday. Seattle Sheraton. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave, Suite 900, Seattle 98121. (206) 623-4801.

The research and clinical leader

VALIUM® Ⓥ diazepam/Roche

Valium® (diazepam/Roche) Ⓥ Tablets
Valrelease™ (diazepam/Roche) Ⓥ slow-release Capsules
Injectable Valium® (diazepam/Roche) Ⓥ

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral forms* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

The effectiveness of diazepam in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications: Tablets or capsules in children under 6 months of age; known hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of predisposition to habituation/dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because their use is rarely a matter of urgency and because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

ORAL: Advise patients against simultaneous ingestion of alcohol and other CNS depressants.

Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral forms adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Injectable Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs.

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status. Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of diazepam, *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed and tolerated).

The clearance of diazepam and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

INJECTABLE: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, observed in patients during and after diazepam therapy are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Dosage: Individualize for maximum beneficial effect.

ORAL: *Adults:* Anxiety disorders, relief of symptoms of anxiety—Valium tablets, 2 to 10 mg b.i.d. to q.i.d.; or 1 or 2 Valrelease capsules (15 to 30 mg) daily. Acute alcohol withdrawal—tablets, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; or 2 capsules (30 mg) the first 24 hours, then 1 capsule (15 mg) daily as needed. Adjunctively in skeletal muscle spasm—tablets, 2 to 10 mg t.i.d. or q.i.d.; or 1 or 2 capsules (15 to 30 mg) once daily. Adjunctively in convulsive disorders—tablets, 2 to 10 mg b.i.d. to q.i.d.; or 1 or 2 capsules (15 to 30 mg) once daily.

Geriatric or debilitated patients: Tablets—2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated (see Precautions). Capsules—1 capsule (15 mg) daily when 5 mg oral Valium has been determined as the optimal daily dose.

Children: Tablets—1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use in children under 6 months). Capsules—1 capsule (15 mg) daily when 5 mg oral Valium has been determined as the optimal daily dose (not for use in children under 6 months).

INJECTABLE: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V., and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension. Dialysis is of limited value.

How Supplied:

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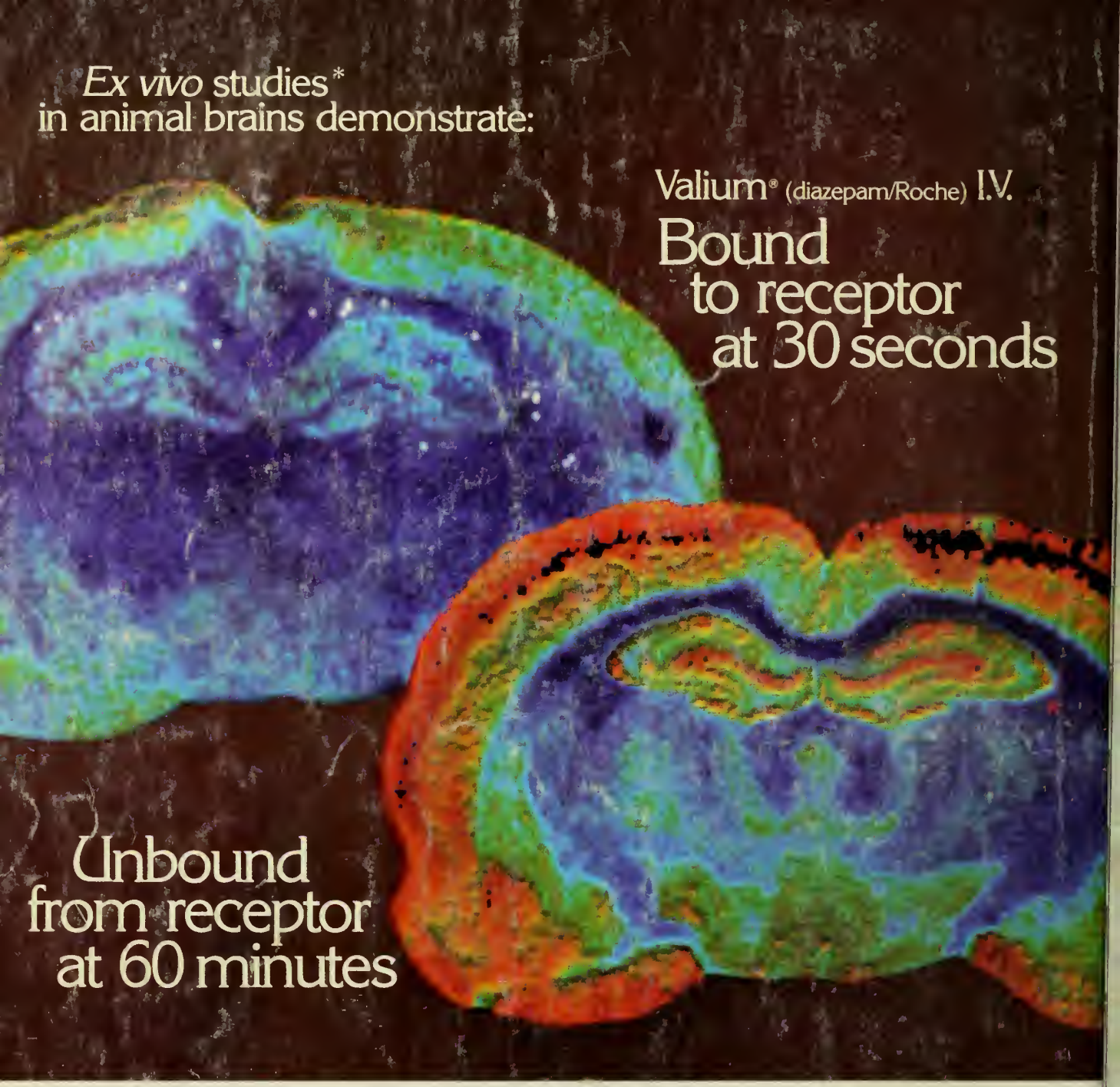

The significance:

Occupancy of brain receptor sites may be more relevant than plasma half-life in explaining duration of pharmacologic action.

Although the exact nature of the correlation between benzodiazepine binding sites and receptors is still being defined, there is considerable evidence supporting the relationship.

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See reverse side for summary of product information.

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The Western Journal of Medicine

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Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

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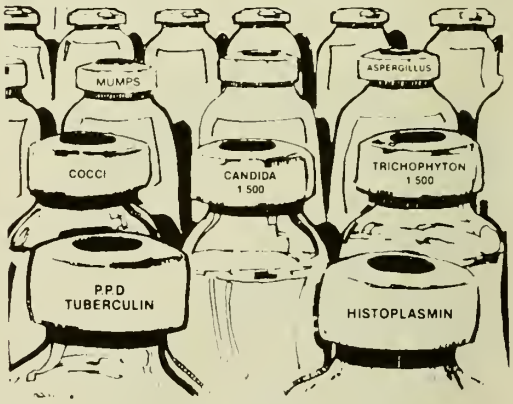

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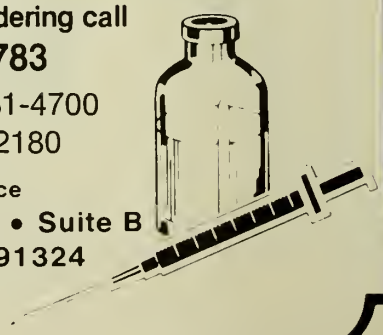

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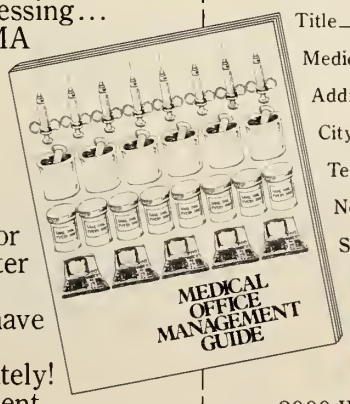

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DRUG INTERACTIONS **Wytensin** was not demonstrated to cause drug interactions when given with other drugs, e g , digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials However, potential for increased sedation when given concomitantly with CNS depressants should be noted

DRUG/LAB TEST INTERACTIONS No lab test abnormalities were identified with **Wytensin** use

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY No evidence of carcinogenic potential emerged in rats during a two-year oral study with **Wytensin** at up to 9 5 mg/kg/day, i.e , about 10 times maximum recommended human dose In the Salmonella microsome mutagenicity (Ames) test system, **Wytensin** at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture In another eukaryotic system, *Saccharomyces cerevisiae*, **Wytensin** produced no activity in an assay measuring induction of repairable DNA damage Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9 6 mg/kg), suggesting impairment of fertility Fertility of treated males (9 6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy

PREGNANCY Pregnancy Category C WYTENSIN® MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN A teratology study in mice indicated possible increase in skeletal abnormalities when **Wytensin** is given orally at doses 3 to 6 times maximum recommended human dose of 1 0 mg/kg These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits However, increased fetal loss has been observed after oral **Wytensin** given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg) Reproductive studies in rats have shown slightly decreased live-birth-indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6 4 and 9 6 mg/kg There are no adequate, well-controlled studies in pregnant women **Wytensin** should be used during pregnancy only if potential benefit justifies potential risk to fetus

NURSING MOTHERS Because no information is available on **Wytensin** excretion in human milk, it should not be given to nursing mothers

PEDIATRIC USE Safety and effectiveness in children less than 12 years of age have not been demonstrated, use in this age group cannot be recommended

Adverse Reactions: Incidence of adverse effects was ascertained from controlled clinical studies in U S and is based on data from 859 patients on **Wytensin** for up to 3 years There is some evidence that side effects are dose-related Following table shows incidence of adverse effects in at least 5% of patients in study comparing **Wytensin** to placebo, at starting dose of 8 mg b i d

Adverse Effect	Placebo (%) n = 102	**Wytensin** (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20% Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less Cardiovascular—chest pain, edema, arrhythmias, palpitations Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort Central nervous system—anxiety, ataxia, depression, sleep disturbances ENT disorders—nasal congestion Eye disorders—blurring of vision Musculoskeletal—aches in extremities, muscle aches Respiratory—dyspnea Dermatologic—rash, pruritus Urogenital—urinary frequency, disturbances of sexual function Other—gynecomastia, taste disorders

Drug Abuse and Dependence: No dependence or abuse has been reported

Overdosage: Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic Vital signs and fluid balance should be carefully monitored Adequate airway should be maintained and, if indicated, assisted respiration instituted No data are available on **Wytensin** dialyzability

Dosage and Administration: Individualize dosage A starting dose of 4 mg b i d is recommended, whether used alone or with a thiazide diuretic Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response Maximum dose studied has been 32 mg b i d , but doses this high are rarely needed

How Supplied: **Wytensin** Tablets, 4 mg and 8 mg, bottles of 100

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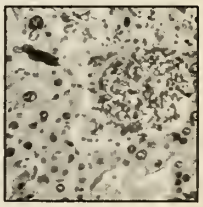

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(Continued from adjacent page)

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNI-MATIC® unit-dose packs of 100 tablets.

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Princeton, NJ 08540 524-503
Issued: January 1984

ACE INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme
†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function*, Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on adjacent page)

INNOVATORS IN CARDIOVASCULAR MEDICINE

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Capoten

(captopril tablets)

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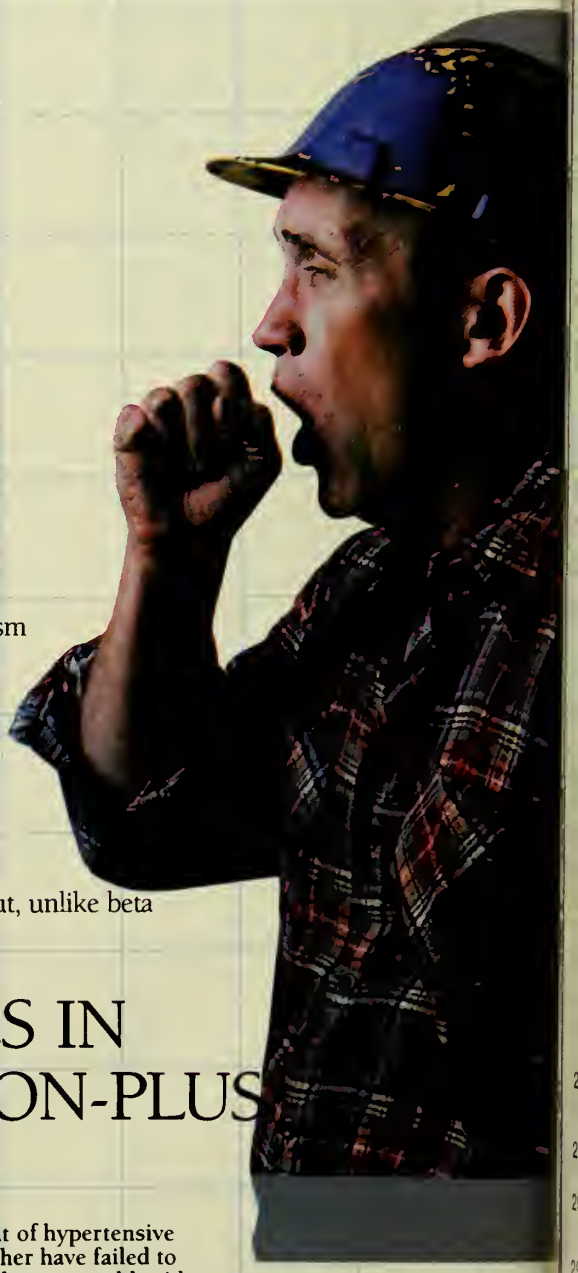
FOR HYPERTENSION†-PLUS

Patients treated for hypertension† may have other disorders that commonly coexist with elevated blood pressure—approximately 14% may have diabetes, 7% asthma, 13% heart failure.[1] Unlike many other antihypertensive agents, CAPOTEN, because of its unique mode of action, is not contraindicated for use in any of these coexisting conditions that frequently complicate hypertension management:

+ DIABETES† (14%)

CAPOTEN does not mask the warning symptoms of hypoglycemia, unlike some beta blockers



+ BRONCHOSPASTIC PULMONARY DISEASE† (7%)

CAPOTEN rarely causes bronchospasm

+ HEART FAILURE† (13%)

CAPOTEN improves cardiac output, unlike beta blockers

MORE PLUSES IN HYPERTENSION-PLUS

*Angiotensin Converting Enzyme

†CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.

Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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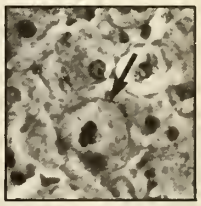

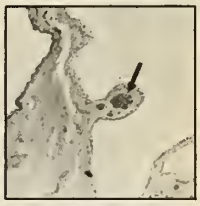

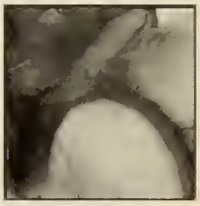

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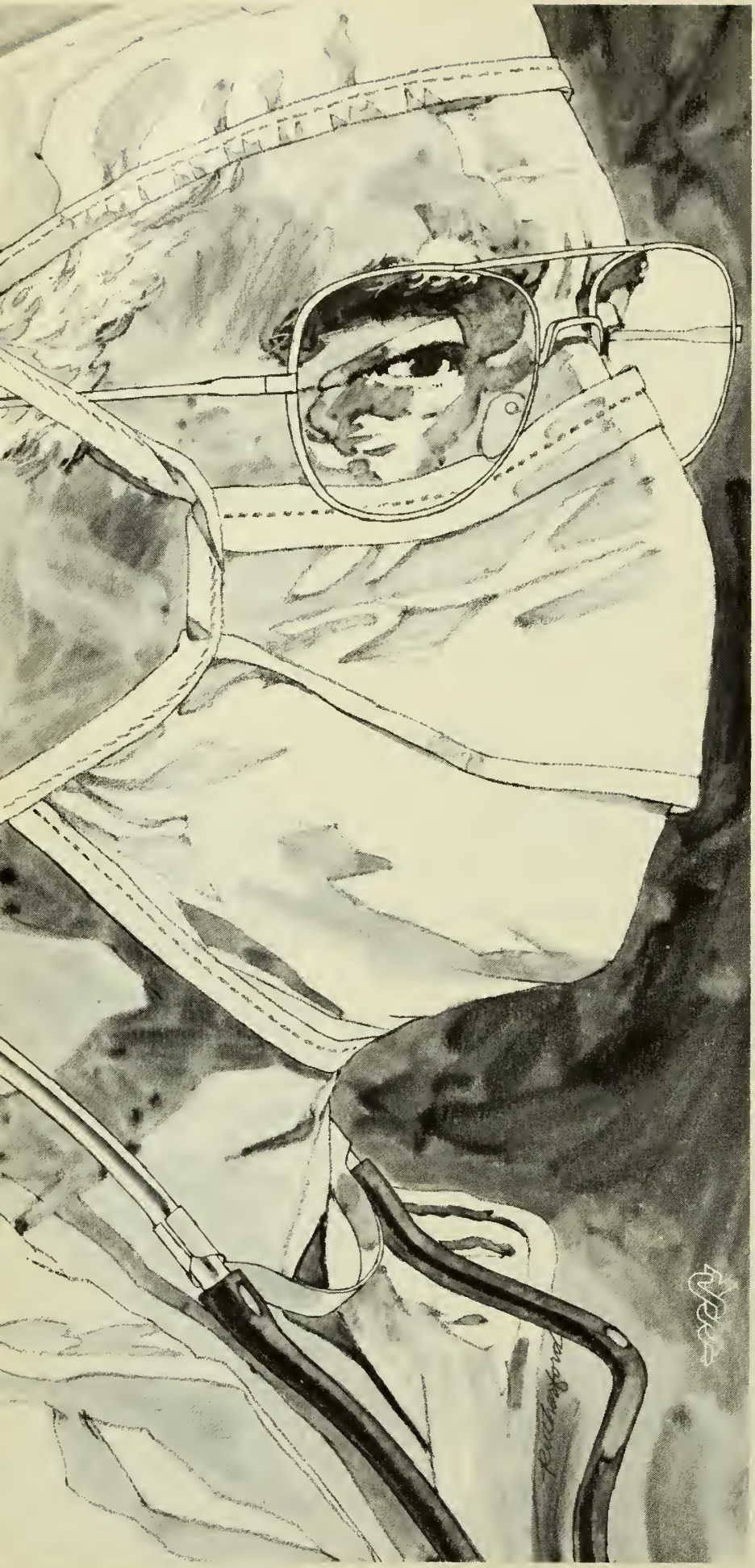

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Active duodenal ulcer healing through effective acid control

- ☐ Control of gastric acid secretion with one tablet b.i.d. It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers.
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- ☐ No interaction with warfarin, theophylline or diazepam.
- ☐ Headache has been reported in about 3% of patients.

*37% of patients can be expected to show complete healing at the end of two weeks; if healing is confirmed, treatment can be discontinued.

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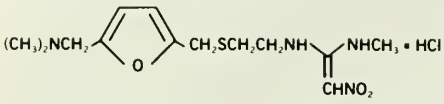
Please see complete prescribing information on the following page.

The first advance in H_2-antagonist therapy

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTION: The active ingredient in ZANTAC* Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure:



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLOGY: ZANTAC* (ranitidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. Effects on acid secretion:

ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC* on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg 75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. Effects on other gastrointestinal secretions:

Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.

Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. Other pharmacological actions:

a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. Pharmacokinetics:

ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Duodenal Ulcer

In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC*-treated patients as shown below:

	ZANTAC* + Number Entered	Healed/ Evaluable	Placebo + Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid Ulcer Healed	Ulcer Not Healed
ZANTAC*	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions

(such as Zollinger-Ellison Syndrome)

ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIONS AND USAGE:

ZANTAC* (ranitidine hydrochloride) is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC* (ranitidine hydrochloride).

PRECAUTIONS:

General

1. Symptomatic response to ZANTAC* therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests

False positive tests for urine protein with Multistix* may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction

Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility

There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. Coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC* (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS

Headache has been found to be more frequent in ZANTAC*-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC* in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Duodenal Ulcer

The current recommended adult oral dosage of ZANTAC* for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions

(such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED

ZANTAC* Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Glaxo

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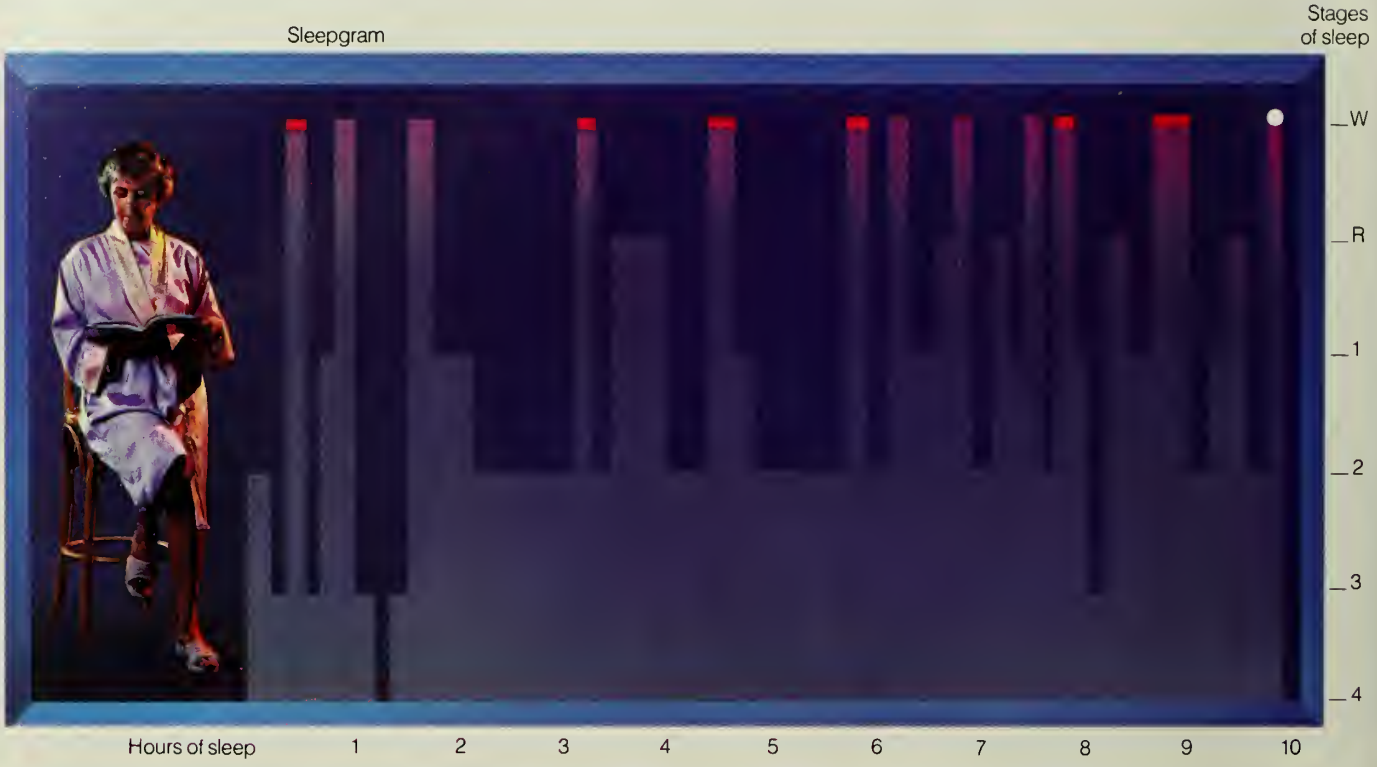
DISRUPTIVE
DISTRESSING
DISABLING

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

= objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

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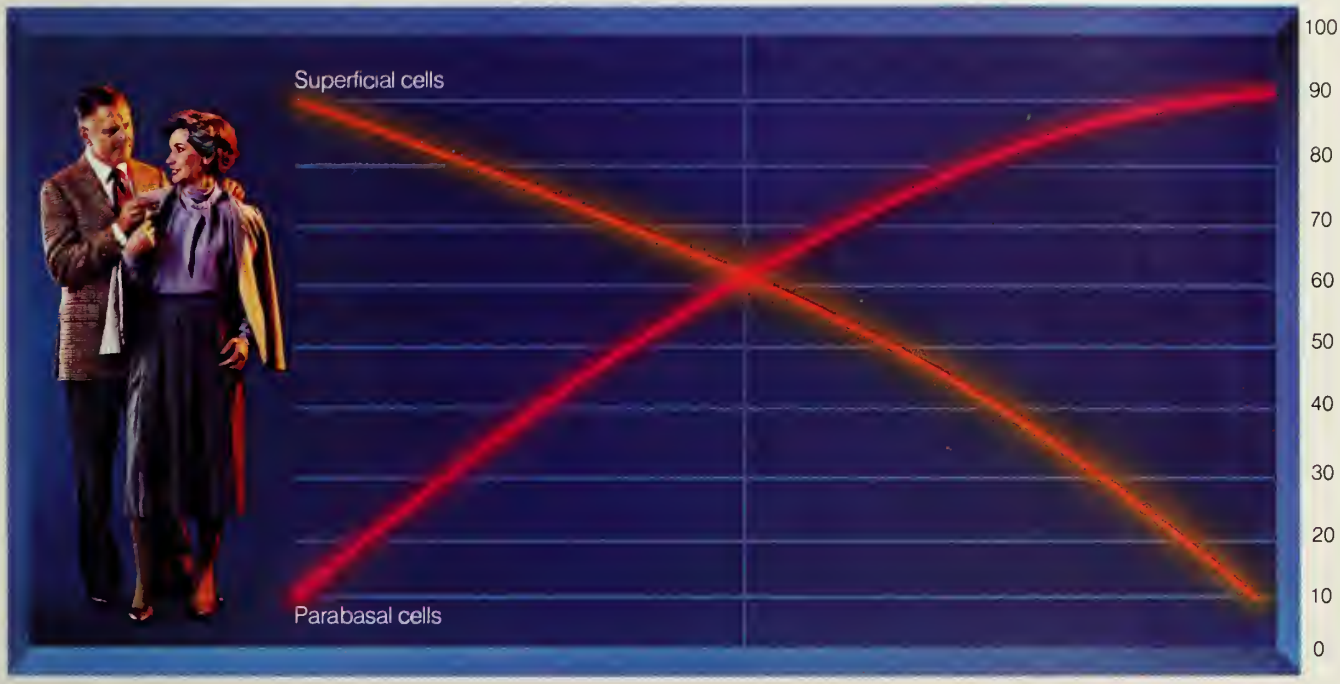
THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

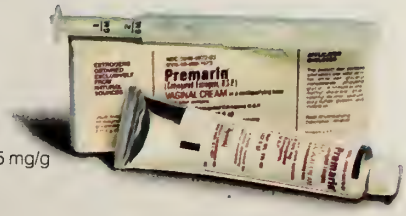
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

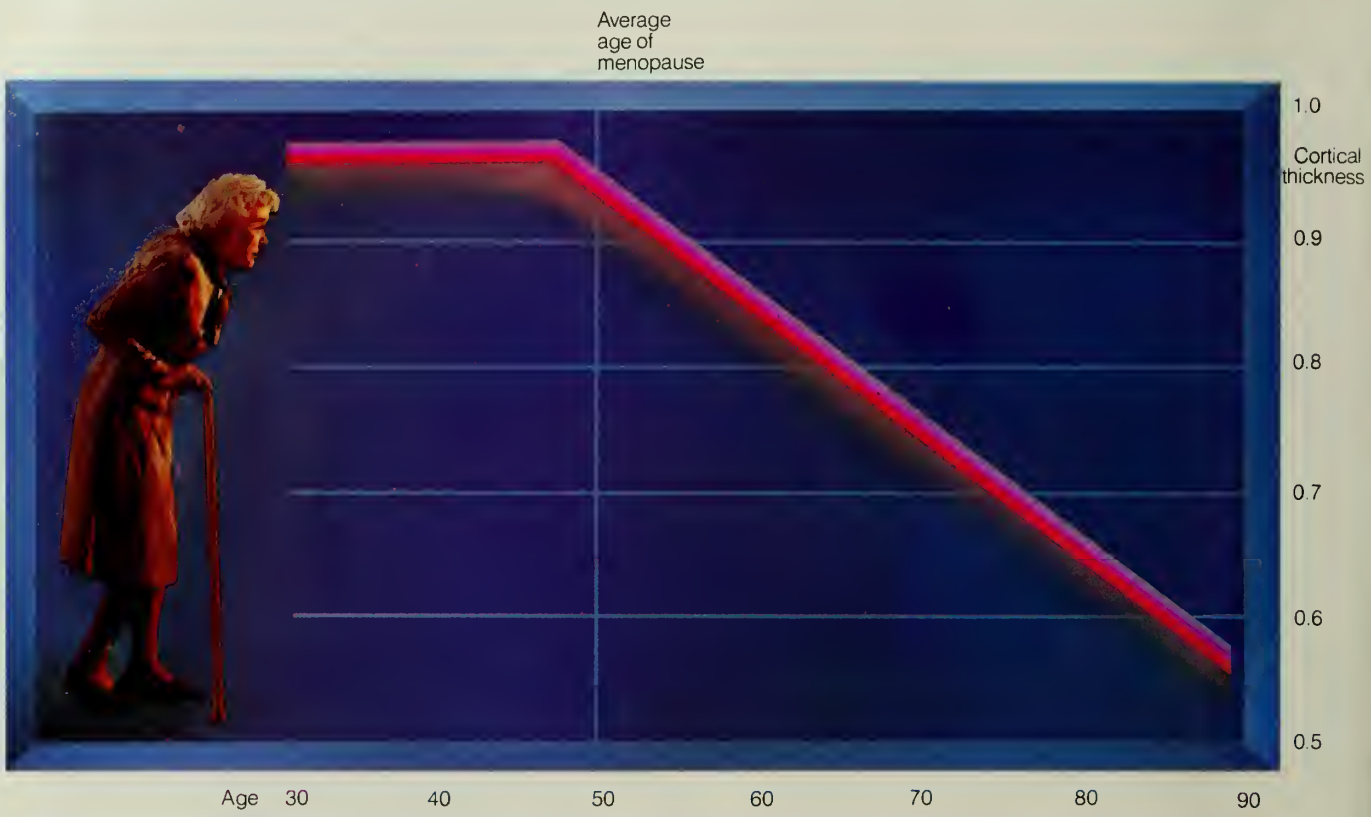
FOR ATROPHIC VAGINITIS

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0 625 mg/g

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

Please see last page for brief summary of prescribing information.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis.

8RIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT 8E USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: 8ased on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. 8reast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT 8EEN SHOWN TO 8E EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT 8EEN SHOWN TO 8E EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE 8OXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See 8oxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

8enign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (T8G) leading to increased circulating total thyroid hormone, as measured by P8I, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated T8G; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued, erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube.

REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al: Estrogen replacement therapy: Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull*, June 1983, pp 1-5. 4. Ayers LJ: The maturation index: A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G: Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ: Age, estrogen, and bone density. *Clin Obstet Gynecol* 1981;24:203-218. 7. Gordan GS, Picchi J, Roof 8S, et al: Postmenopausal osteoporosis. *Am Fam Physician* 1973;8:74-83. 8. US 8ureau of the Census, *Statistical Abstract of the United States* 1982-83, ed. 103. Washington, DC, US Dept of Commerce, 1982, p 25. 9. Mallette LE: Osteoporosis: Approaching treatment with optimism. *Postgrad Med* 1982;72:271-278.

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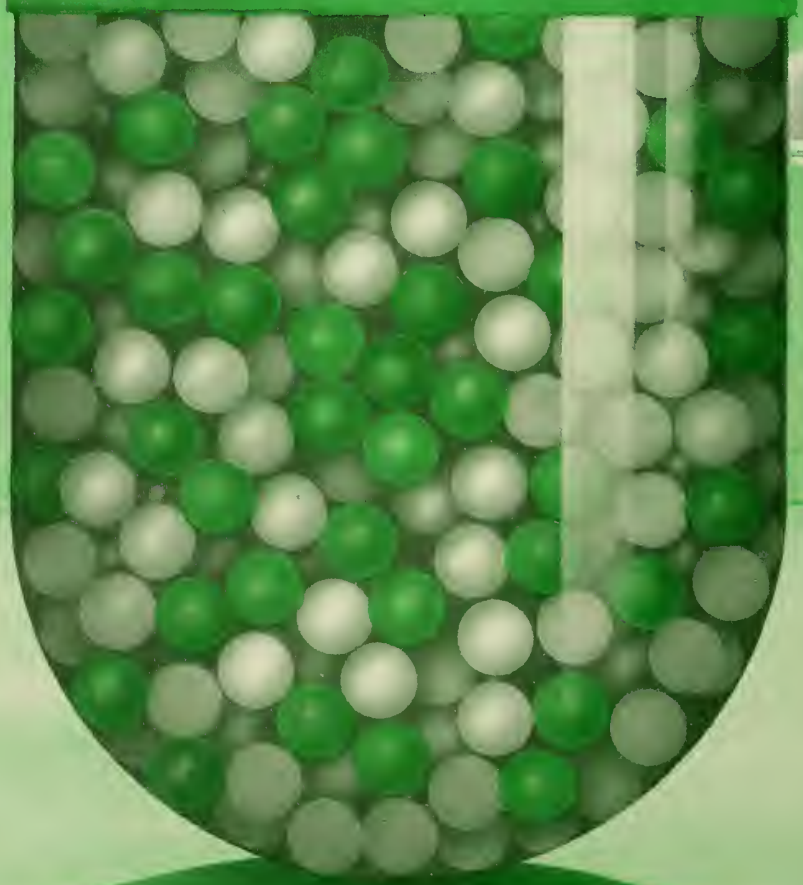

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Before prescribing, see complete prescribing information. The following is a brief summary.
DESCRIPTION: Each sustained release capsule contains 12 mg of Chlorpheniramine Maleate, USP and 75 mg of Phenylpropanolamine Hydrochloride, USP in a base to provide prolonged activity.
INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).
CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis. Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.
WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.
Usage In pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.
PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal function impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, Alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.
ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with Chlorpheniramine Maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis histeria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.
DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.
OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.
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ALLERGY AND IMMUNOLOGY

February 29-March 3—**7th Annual Course: Immunology and Clinical Practice of Allergy.** UCSD. Wednesday-Saturday. 20 hrs.

March 1-3—**8th Annual Course: Immunology and the Clinical Practice of Allergy.** American Academy of Allergy and Immunology and UCSD at San Diego Hilton Hotel, Mission Bay, San Diego. Thursday-Saturday. Contact: UCSD.

June 13-15—**Contemporary Aspects of Clinical Immunology.** American Society of Clinical Pathologists at San Diego. Wednesday-Friday. 18.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

ANESTHESIOLOGY

February 18-19—**American Society of Anesthesiologists Regional Refresher Course** at San Francisco Hilton Hotel. Saturday-Sunday. Contact: ASA, 515 Busse Hwy, Park Ridge, IL 60068. (312) 825-5586.

February 18-24—**12th Obstetric Anesthesia Conference.** Ohio State University Hospital, Dept. of Anesthesiology at Sheraton Waikiki Hotel, Waikiki, HI. One week. 20 hrs. Contact: The Ohio State University Hospital, Dept. of Anesthesiology, 410 W. 10th Ave., Columbus, Ohio 43210. (614) 421-8487.

March 8-11—**Anesthesia for Obstetrics.** UCSF. Thursday-Sunday.

April 9-13—**Critical Care Medicine 10th Hawaiian Seminar.** California Society of Anesthesiologists at Sheraton Kauai Hotel, Poipu Beach, Kauai. Monday-Friday. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

June 14-17—**Annual Scientific Meeting of the California Society of Anesthesiologists** at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

CANCER

February 15-17—**Clinical Laboratory Molecular Analyses: New Strategies in Autoimmunity, Cancer, and Virology.** Scripps Clinic and Research Foundation and Mayo Clinic at Vacation Village, San Diego. Wednesday-Friday. 21 hrs. $290. Contact: Dianne Tisue, Dept. of Academic Affairs, 400S, Scripps Clinic and Research Fndn, 10666 N. Torrey Rd., La Jolla 93037.

February 24-25—**Intra-Arterial and Intracavitary Chemotherapy 1984.** UCSD at Holiday Inn at the Embarcadero, San Diego. Friday-Saturday. 14 hrs. $250.

March 1-3—**UCLA Winter Oncology Conference.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Thursday-Saturday. 18.5 hrs. $360.

March 31—**Controversies in Breast Cancer.** St. Agnes Medical Center, Fresno. Saturday. 7 hrs. $40. Contact: Carol Witham, ART, Coord. Tumor Reg., Cancer Program, St. Agnes Med. Ctr., 1303 E. Herndon Ave., Fresno 93710. (209) 449-3570.

May 18-20—**The Primary Care Physician and Cancer.** UCSD at Vacation Village, San Diego. Friday-Sunday.

CARDIOLOGY

February 15-18—**Cardiopulmonary Management of the Critically Ill Patient.** American College of Chest Physicians at Sheraton Palace Hotel, San Francisco. Wednesday-Saturday. Contact: ACCP, Div. of Ed., 911 Busse Hwy, Park Ridge, IL 60068.

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine. 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

JUST ONCE-DAILY FOR INITIAL THERAPY IN HYPERTENSION

Unique, once-daily formulation providing comprehensive cardiovascular protection

INDERAL LA offers the antihypertensive and cardiovascular benefits of INDERAL–with the additional advantage of convenient, single daily dosage. With a unique controlled-release formulation, INDERAL LA (propranolol HCl) provides sustained plasma levels and consistent, 24-hour beta blockade.

Smooth 24-hour blood pressure control

In controlled clinical studies, INDERAL LA effectively maintained systolic and diastolic blood pressure reductions with single daily dosing.

Avoids the potassium loss associated with diuretics

INDERAL LA controls blood pressure without the problem of hypokalemia often associated with long-term diuretic therapy. Like conventional INDERAL, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

THE ONE™ TO COUNT ON

Start with 80 mg once daily...

Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. When converting patients from other beta blockers, including INDERAL tablets, start with the nearest milligram equivalent of INDERAL LA once daily and evaluate clinical results to determine if dosage adjustment is necessary. For arrhythmias, use conventional INDERAL (propranolol HCl) tablets.

The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

Please see next page for brief summary of prescribing information.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

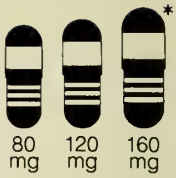
Ayerst®

The one to count on for HYPERTENSION, ANGINA and prevention of MIGRAINE.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR)*
INDERAL® LA BRAND OF propranolol hydrochloride
(Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta-blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized*. The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized*. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized*. The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

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Ayerst AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 191)

February 16-18—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology and Orange Coast Heart Institute, Hoag Memorial Hospital Presby. at Newport Beach Marriott Hotel and Tennis Club, Newport Beach. Thursday-Saturday. Contact: Registration Secretary, Extramural Programs Department, ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

February 23-25—**Duplex Scanning.** Scripps Clinic and the Institute for Medical Studies at San Diego. Thursday-Saturday. 15 hrs. Contact: Kim Stroich, IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

March 2-4—**Cardiovascular Disease: Non-Invasive Diagnostic Methods and Cardiac Rehabilitation.** International Medical Education Corporation at Islandia Hyatt, San Diego. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

March 4-7—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday. $15 hrs. $225.

March 9-11—**Pathophysiology and Techniques of Cardiopulmonary Bypass IV.** See Surgery, March 9-11.

March 16-18—**Advanced Cardiovascular Diagnostic, Rehabilitation and Patient Follow-up Methods.** International Medical Education Corporation at St. Francis Hotel, San Francisco. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

March 16-18—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Marriott Hotel, Palm Springs. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

March 18-24—**Current Drug Usage in Cardiac Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine sailing at Maui, Molokai, and Lanai, HI. One week. 24 hrs. Contact: Richard F. Paris, MD. (208) 788-4995.

March 19-20—**Advanced Cardiac Life Support.** See Emergency Medicine, March 19-20.

March 24—**Reflections on Cardiac Surgery.** See Surgery, March 24.

April 18-20—**Moguls of Cardiology.** American Heart Association, Golden Empire Chapter at Caesars Tahoe, Lake Tahoe. Wednesday-Friday. Contact: AHA, Golden Empire Chapt., P.O. Box 160126, 1727 30th St., Sacramento 95816. (916) 454-0701.

April 28—**50,000 Open-Heart Operations.** See Surgery, April 28.

May 4-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Sheraton Palace, San Francisco. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

May 12—**Cardiac Surgery Research.** See Surgery, May 12.

May 12—**Cardiovascular Symposium.** Marian Medical Center at Holiday Inn, Santa Maria. Saturday. 6 hrs. Contact: Alfred Sanfilippo, MD, Dir. CME, Marian Med. Ctr., 1400 E. Church, Santa Maria 93454. (805) 922-5811, ext. 115.

May 18-20—**Decision Making in Congenital Heart Disease.** Children's Hospital and Health Center and Donald N. Sharp Memorial Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Sunday. 18 hrs. $350. Contact: Congenital Heart Disease, P.O. Box 9494, San Diego 92109. (619) 272-3126.

May 21-22—**Advanced Cardiac Life Support.** See Emergency Medicine, May 21-22.

June 10-13—**Advanced Echocardiography—1984: Interactions with NMR, Digital Angiography and CT Scanning.** American College of Cardiology at San Diego. Sunday-Wednesday. Contact: Reg. Sec., Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 25-27—**Cardiac Morphology: Echocardiographic, Nuclear Imaging, Necropsy Correlations.** American College of Cardiology and Indiana University School of Medicine at Hyatt Lake Tahoe, Incline Village. Monday-Wednesday. Contact: Reg. Sec., Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 25-29—**National Board Review Course in Pulmonary Medicine.** American College of Chest Physicians at Sheraton Palace Hotel, San Francisco. Monday-Friday. 28 hrs. Contact: Dept. of Ed., ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (312) 698-2200.

August 12-17—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

EMERGENCY MEDICINE

February 26-March 2—**Emergency Medicine: 1984 7th Annual UCD Winter Conference.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 7 hrs. $345.

March 4-9—**5th Annual Mammoth Mountain Emergency Medicine Ski Conference.** Medical Conferences, Inc., UCI and Orange County Emergency Department Nurses Association at Mammoth Lakes. Sunday-Friday. 20 hrs. $325. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 650-4156.

March 5-8—**22nd Annual Critical Care Medicine Symposium.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday. 25 hrs. $395.

March 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at La Jolla Village Hotel, La Jolla. Monday-Friday.

March 14-16—**Advances in Controversies in Acute Respiratory Failure.** California Thoracic Society at Santa Barbara Biltmore Hotel, Santa Barbara. Wednesday-Friday. Contact: CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 19-20—**Advanced Cardiac Life Support.** Emergency Care Education Center, Inc., Emergency Department Physicians, Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

April 7-14—**Critical Care Medicine.** USC at Mauna Lani, HI. One week.

April 11—**Cardiac Emergencies.** LLU. Wednesday. 4 hrs. $50.

April 12-14—**Current Emergency Diagnosis and Treatment.** UCSF. Thursday-Saturday. 16 hrs. $260.

April 14-21—**Problems and Controversies in Emergency Medicine.** UCSD and Scripps Memorial Hospital, Encinitas at Maui. One week. 21 hrs. $335. Contact: UCSD.

April 30-May 4—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday.

May 4-5—**1st Annual Emergency Symposium.** Southern California Kaiser-Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. 11 hrs. $150. Contact: Dept. of Clinical Services, SCKPM Care Program, 4747 Sunset Blvd., Los Angeles 90027.

May 21-22—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

June 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 33 hrs.

June 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton Wharf, San Francisco. Monday-Friday. $425.

(Continued on Page 199)

SOME MALPRACTICE INSURANCE COMPANIES ARE BIG FLAG-WAVERS

You'd be surprised how many insurance companies are quick to surrender when it comes to fighting a malpractice suit. It's simply cheaper, faster and easier to make a settlement.

But where does that leave you? You may not be armed with the proper ammunition to fight, because your policy may give you less than you think.

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age. Does your insurance company give you the right to say yes or no to a settlement? Some don't. Some will tell you they do, but they may limit your coverage to the amount they'll settle for. If you still want to fight—and end up losing—anything over that settlement figure comes out of your pocket.

At ICA, we know your reputation is on the line. And that's worth fighting for. We'll jump to your defense from the moment you suspect a problem. Not with claims adjusters. But with an experienced staff of claims attorneys who'll work to stop a lawsuit before it starts.

If a suit does occur, we'll assemble the toughest legal counsel available in your area. And we'll fight until we either win or exhaust every legal option. But we'll never settle without your consent.

No one should take away your right to defend yourself. So, if you ever have to send up a red flag, we won't wave a white one. Contact Insurance Corporation of America, ICA Center, 4295 San Felipe, Box 56308, Houston, Texas 77256. Phone 1-800-231-2615; in Texas, 1-800-392-9702.

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THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

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(Continued from Page 195)

July 6-8—**Trauma and CPR Update—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 16-20—**Postgraduate Institute for Emergency Physicians.** UCSD. Monday-Friday. 33 hrs.

July 30-31—**Advanced Cardiac Life Support.** Emergency Care Education Center, Emergency Department Physicians, and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina Del Rey 90291. (213) 822-1312.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** American College of Obstetrics and Gynecology at Hotel del Coronado, Coronado. Wednesday-Friday. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington DC 20024.

August 23-26—**Wilderness Emergency Care—Mt. Shasta Summit Expedition.** Mercy Medical Center, Redding at Mt. Shasta. Thursday-Sunday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

August 27-31—**Topics in Emergency Medicine.** UCSF at San Francisco. Monday-Friday. $425.

INTERNAL MEDICINE

February 17-18—**Infectious Disease.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

February 17-19—**Mind and Metabolism: Regulation and Self-Regulation of the Autonomic and Central Nervous System.** UCLA. Friday-Sunday.

February 23-26—**State of the Art in Neurosciences.** Federation of Western Societies of Neurological Science at Silverado Country Club, Napa. Thursday-Sunday. 18 hrs. Contact: FWSNS, 525 Hurlingham Ave., San Mateo 94402. (415) 340-9084.

March 2—**10th Annual Diabetes Program.** UCD at Sacramento Inn, Sacramento. Friday.

March 7-10—**Office Endocrinology.** UCSF at Hyatt Lake Tahoe. Wednesday-Saturday. 15 hrs. $225.

March 8-10—**1984 International Symposium on Viral Hepatitis.** UCSF at Hilton, San Francisco. Thursday-Saturday.

March 8-10—**Advanced Nephrology and Hypertension: Nephrology for the Consultant.** Annenberg Center for Health Sciences and UCSD at Annenberg Center, Rancho Mirage. Thursday-Saturday. 18 hrs. Contact: Annenberg Center for Health Sciences, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 340-3911, ext. 1661.

March 14—**Arthritis of the Single Joint.** LLU. Wednesday. $50.

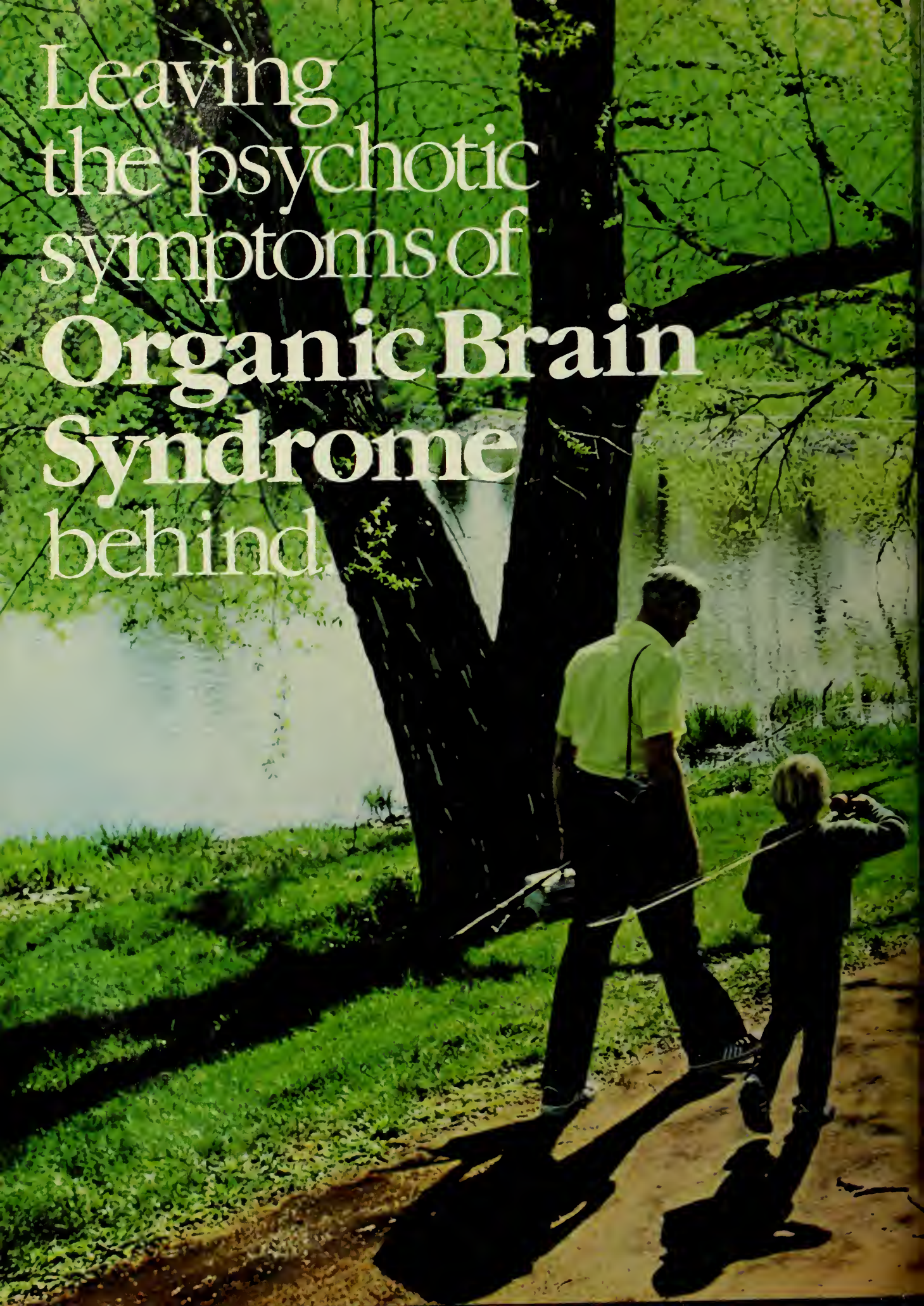
March 15-16—**New Concepts in Hemophilia Treatment.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Friday.

March 15-17—**4th International Conference in Coccidioidomycosis.** American College of Chest Physicians at Hyatt Islandia Hotel, San Diego. Thursday-Friday. Contact: AACP, Div. of Ed., 911 Busse Hwy, Park Ridge, IL 60068.

March 15-17—**Frontiers in Rheumatology.** Annenberg Center for Health Sciences of the Eisenhower Medical Center, Rancho Mirage. Thursday-Saturday. 16 hrs. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

March 23—**11th Annual Neurology Symposium.** Southern California Kaiser-Permanente Medical Care Program at Biltmore Hotel, Los Angeles. Friday. Contact: Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

(Continued on Page 204)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the psychotic
symptoms of
Organic Brain
Syndrome
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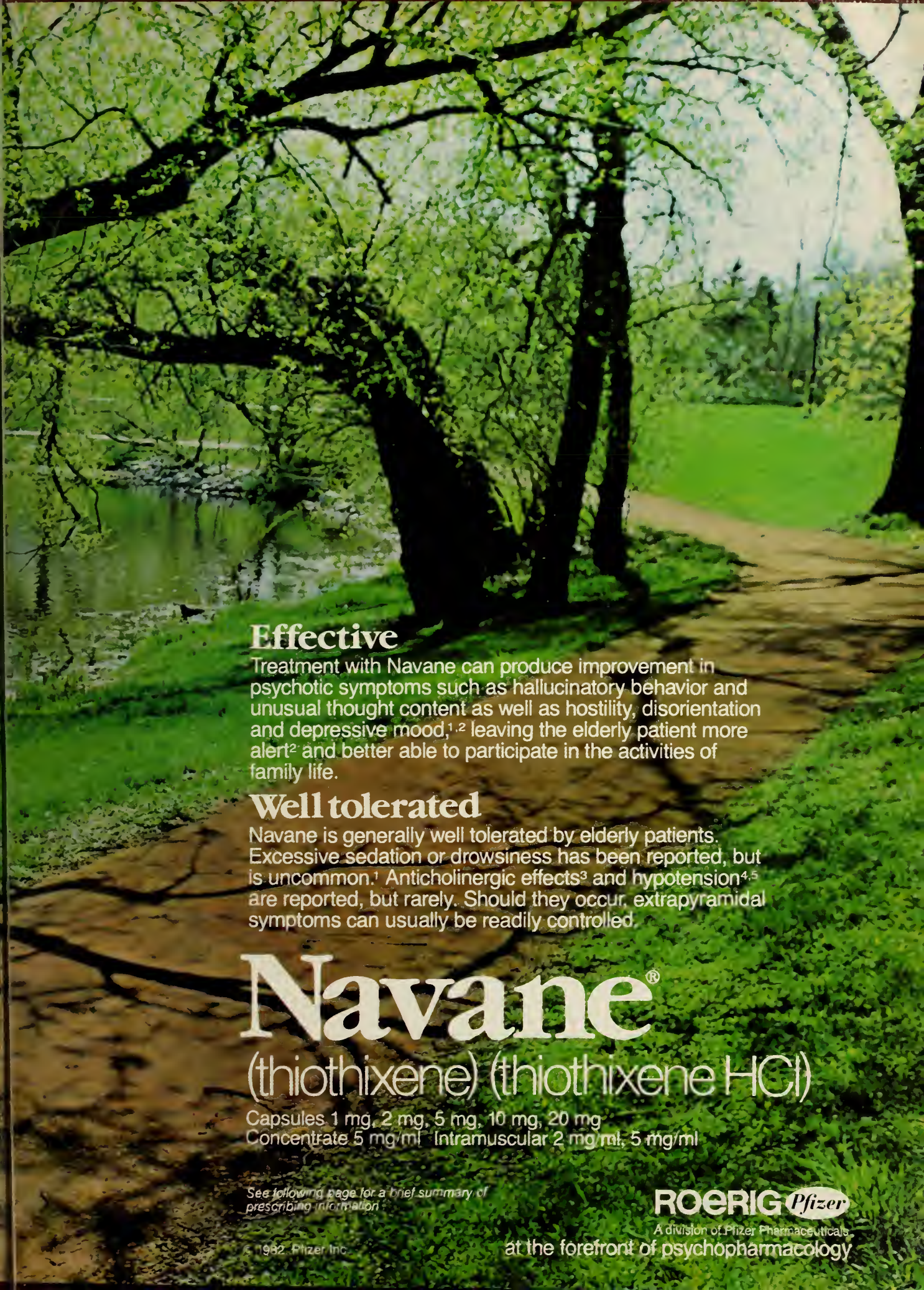
Effective
Treatment with Navane can produce improvement in psychotic symptoms such as hallucinatory behavior and unusual thought content as well as hostility, disorientation and depressive mood,[1,2] leaving the elderly patient more alert[2] and better able to participate in the activities of family life.
Well tolerated
Navane is generally well tolerated by elderly patients. Excessive sedation or drowsiness has been reported, but is uncommon.[1] Anticholinergic effects[3] and hypotension[4,5] are reported, but rarely. Should they occur, extrapyramidal symptoms can usually be readily controlled.
Navane®
(thiothixene) (thiothixene HCl)
Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
Concentrate 5 mg/ml Intramuscular 2 mg/ml, 5 mg/ml
See following page for a brief summary of prescribing information.
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Navane®
(thiothixene) (thiothixene HCl)

References 1. Util TM, Unverdi C, Wohlrade J, et al. Drug therapy of psychosis associated with organic brain syndrome. Presented as a Scientific Exhibit at the American Public Health Association Centennial, Atlantic City, New Jersey, November 12-16, 1972. 2. Katz MM, Util TM. Video methodology for research in psychopathology and psychopharmacology. *Arch Gen Psychiatry* 31:204-210, 1974. 3. Ketai R: Psychotropic drugs in the management of psychiatric emergencies. *Postgraduate Medicine* 58:87-93, 1975. 4. Birkett DP, Hirschfield W, Simpson GM. Thiothixene in the treatment of diseases of the senium. *Curr Ther Res* 14:775-779, 1972. 5. Data on file at Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Usage in Pregnancy*—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels, the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane. These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane (thiothixene). Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

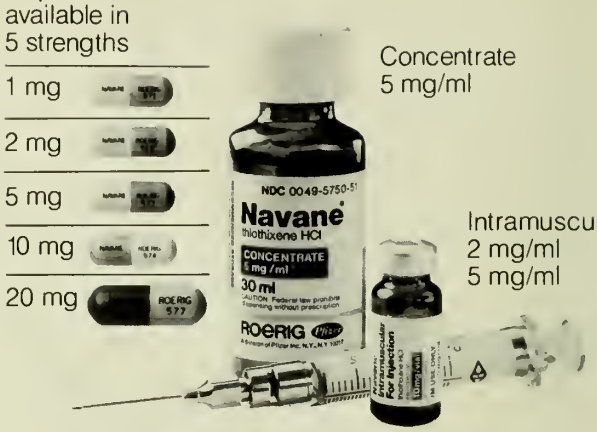
Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Capsules available in 5 strengths



There is no known effective treatment for tardive dyskinesia, antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear.

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Hepatic effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene) have been reported.

Hematologic effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other adverse reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution, Navane For Injection—Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules, Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

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(Continued from Page 199)

March 26-27—**Circulatory Problems in the Aging Adult.** Eisenhower Medical Center at Annenberg Center, Rancho Mirage. Monday-Tuesday. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 621-7322.

March 29-30—**1984 Updates: Medical and Behavioral Treatment.** See Of Interest To All Physicians, March 29-30.

March 30—**A Focus on CCPD for Adults and Children.** UCLA at Century Plaza Hotel, Los Angeles. Friday. 7 hrs. $35.

March 31-April 7—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Hotel, Mauna Kea, HI. One week.

April 4—**Thyroid '84.** The Hospital of the Good Samaritan at Hyatt Regency Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, Coordinator of Symposia, 616 S. Witmer St., Los Angeles 90017. (213) 977-2352.

April 12-14—**Surgery of the Upper Extremity in Rheumatoid Arthritis.** Eisenhower Medical Center at Annenberg Center, Rancho Mirage. Thursday-Saturday. 12 hrs. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

April 28-May 5—**New Concepts in Gastroenterology: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Poplin Creek Estate, Ojai. One week. 24 hrs. Contact: Richard F. Paris, MD. (208) 788-4995.

May 7-11—**Advances in Internal Medicine.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

May 7-11—**Clinical Microbiology Update.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 29.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-1336, ext. 129.

May 28-30—**Endocrinology in Clinical Practice.** UCSF. Monday-Wednesday.

June 13-15—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Stanford Court Hotel, San Francisco. Wednesday-Friday. $375.

June 18-22—**Advances in Internal Medicine.** UCSF at Hyatt Regency, San Francisco. Monday-Friday. $465.

June 22-24—**Update on Cardiovascular Drugs—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 7-14—**32nd Annual Intensive Review of Internal Medicine.** USC. One week. $475.

July 20-22—**Infectious Disease.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 29-August 1—**Biomedical Ethics—Wilderness Horseback Conference.** Mercy Medical Center, Redding at Trinity Alps Wilderness. Sunday-Wednesday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

OBSTETRICS AND GYNECOLOGY

February 15-17—**Common Problems in Obstetrics.** American College of Obstetrics and Gynecology at Riviera Hotel, Las Vegas. Wednesday-Friday. 16 hrs. Contact: ACOG Registrar, Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

February 16-18—**Advanced Fetal Heart Rate Monitoring.** Memorial Hospital Medical Center and UCI at Sheraton-Waikiki, Oahu. Thursday-Saturday. 10 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801-1428.

February 18—**Endometriosis Update: 1984.** Scripps Clinic and Research Foundation, La Jolla. Saturday. Contact: Dianne Tisue: Conf. Coord., Scripps Clinic and Research Fndn, 10666 N. Torrey Pines Rd., La Jolla 92037.

February 25—**Office Gynecology.** UCLA. Saturday.

March 8-11—**Anesthesia for Obstetrics.** See Anesthesia, March 8-11.

March 14-17—**Contemporary Obstetrics: A Guide to the Physician in Practice.** March of Dimes Birth Defects Foundation, Orange County Chapter, UCI and St. Joseph Hospital at Disneyland Hotel, Anaheim. Wednesday-Saturday. 21.5 hrs. $210. Contact: Michelle S. Wampler, March of Dimes Birth Defects Foundation, Orange County Chapter, Rea Community Center, 661 Hamilton, #650, Costa Mesa 92627-2690.

March 23-25—**Gynecologic Surgery with Emphasis on Gynecologic Urology.** Memorial Hospital Medical Center and UCI at Hilton Riviera, Palm Springs. Friday-Sunday. 15 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

April 8-10—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Tuesday.

April 11-13—**Endocrine Physiology of Pregnancy.** UCSF. Wednesday-Friday.

April 16-19—**Diagnostic Cytology of the Female Genital Tract.** American Society of Clinical Pathologists at San Francisco. Monday-Thursday. 22.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

April 27-28—**29th Annual T. Hart Baker MD Obstetrics and Gynecology Symposium.** Southern California Kaiser-Permanente Medical Care Program at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

May 5-10—**32nd Annual Clinical Meeting of American College of Obstetrics and Gynecology** at San Francisco. Saturday-Thursday. 17 hrs. Contact: ACOG, Registrar, Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

May 13-16—**Recent Advances in Obstretrics and Gynecology.** UCSD. Sunday-Wednesday.

May 30-June 2—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center and UCI at Silverado Country Club and Resort, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

August 9-11—**Basic and Advanced Colposcopy.** American College of Obstetrics and Gynecology at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E., 600 Maryand Ave., SW, Washington, DC 20024.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

OPHTHALMOLOGY

March 1-2—**Annual Postgraduate Seminar—Retina and Choroid: Vascular, Inflammatory and Degenerative Disease.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. $375. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Med., Center for Health Sciences, Los Angeles 90024.

March 31—**Modern Ophthalmologic Procedures: ERG, VER, Ultrasonography, Tonography, Eye Movement Analysis, and Octopus Quantitative Perimetry.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $85. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

April 14—**Drug Therapy and Pharmacology Review for Ophthalmologists.** Jules Stein Eye Institute, Los Angeles. Saturday. $85. Contact: Lu Hendricks, Academic Program Admin.,

(Continued on Page 206)

CALIFORNIA MEDICAL ASSOCIATION

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SAN JOAQUIN VALLEY COUNTIES

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March 22–24, 1984

TOPICS

- Rheumatic Diseases
- Degenerative Cortical Diseases
- Melanoma & Other Skin Cancers
- Diseases of Asian Immigrants
- Depression in Children & Adolescents
- New Cardiac Drugs
- Anorexia & Bulimia

GERIATRICS

Hyatt, Lake Tahoe
June 14–16, 1984

TOPICS

- Physiology of Aging
- Multidimensional Assessment
- Nursing Homes
- Immobility
- Transient Ischemic Attacks
- Osteoporosis
- Ethical Issues
- Incontinence
- Falls/Instability

WEST COAST COUNTIES

Doubletree Inn, Monterey
October 25–27, 1984

Update for Primary Care Physicians

The content of these programs has been determined by the educational needs of primary care physicians as perceived and translated by the members of the Planning Committee

☆ ☆ ☆

These programs are accredited for Category I credit for Physicians and Registered Nurses

☆ ☆ ☆

Hotel space is limited — early reservations are suggested.

☆ ☆ ☆

Complete program and hotel information will be sent by return mail.
Use the tear off sheet below or call CMA (415) 863-5522, extension 416.

I plan to attend the following Postgraduate Institute(s):

☐ **San Joaquin Valley Counties**
March 22–24, 1984
Curry Village, Yosemite

☐ **Geriatrics**
June 14–16, 1984
Hyatt, Lake Tahoe

☐ **West Coast Counties**
October 25–27, 1984
Monterey

FEE: $100 for each institute
($150 for non-CMA members)

Please make check payable to
California Medical Association

Name _____ Specialty _____

Address _____

City _____ Zip _____

Number of years out of Medical School _____

Mail to: California Medical Association, 44 Gough Street, San Francisco, CA 94103
Attention: Janice Rigney A program and hotel reservation form will be sent to you.

(Continued from Page 204)

JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

May 12—**Contact Lens Practice in the Mid-80's.** Jules Stein Eye Institute, Los Angeles. Saturday. $100. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

June 7-8—**Practical Office Management of Corneal, External Diseases and Uveitis.** UCSF at Hyatt Regency, San Francisco. Thursday-Friday.

June 8-9—**Microsurgery and Laser Techniques for Glaucoma.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 14 hrs. $500. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024.

June 14-16—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. 18 hrs. $750. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024.

PEDIATRICS

February 21-23—**Common Operative Problems in Children's Orthopaedics.** See Surgery, February 21-23.

March 11-17—**Forefronts in Pediatrics: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine sailing at Maui, Molokai, and Lania, HI. One week. Contact: Richard F. Paris, MD. (208) 788-4995.

March 15-18—**Combined Southern California Pediatric Postgraduate Meeting.** American Academy of Pediatrics, California Chapter 2 at Palm Springs. Thursday-Sunday. Contact: Eve Black, Exec. Sec., P.O. Box 2134, Inglewood 90305. (213) 757-1198.

March 24-25—**Avoiding the Pitfalls of Pediatric Office Orthopaedics.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Saturday-Sunday. 12.5 hrs. $195.

April 6-7—**Annual Pediatrics Program: Focus on the Newborn.** UCD at Capitol Plaza Holiday Inn, Sacramento, Friday-Saturday.

April 25-27—**9th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center and UCI at Hyatt Regency, Long Beach. Wednesday-Sunday. 17 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

April 26-28—**Advances in Pediatrics.** UCSF at Mark Hopkins, San Francisco. Thursday-Saturday.

April 27-29—**Pediatric Infectious Disease.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Friday-Sunday. Contact: AAP, Div. of Cont. Ed., P.O. Box 1034, Evanston, IL 60204.

May 7-11—**The 1984 14th Annual Review of Pediatrics.** USC and Children's Hospital of Los Angeles at Los Angeles. Monday-Friday. 26 hrs. $350. Contact: USC.

May 16—**Los Angeles Pediatric Society Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** See Psychiatry, May 17-18.

June 13—**Seizure Disorders in Infancy and Childhood.** LLU. Wednesday. 4 hrs. $50.

June 28-30—**9th Annual Meeting of the Society for Pediatric Dermatology.** STAN at Caesar's Tahoe, Lake Tahoe. Thursday-Saturday.

PSYCHIATRY

February 17-18—**Family Therapy and Supervision: Creating Contacts of Competence.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 25—**Issues in Interactional Theory and Research.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: Training Programs, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 9-11—**Progress in Treatment of Affective Disorders.** Central California Psychiatry Society at Rio Bravo Resort, Bakersfield. Friday-Sunday. 8 hrs. $100. Contact: Kern County Psychiatric Society, 1901 Truxton Ave., Bakersfield 93301. (805) 327-2021.

March 14-18—**The Development of the Able Mind Revisited.** Southern California Neuropsychiatric Institute at La Quinta Hotel Golf and Tennis Resort, La Quinta. Wednesday-Sunday. 24 hrs. Contact: Gail Waldron, MD, Program Director, SCNI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

March 15-17—**Mid-Life Issues: Stress, Anxiety and Depression.** John A. Burns School of Medicine, University of Hawaii at Hotel InterContinental, Maui. Thursday-Saturday. 13.5 hrs. $200. Contact: Mrs. Dee Chang, CME, Educational Specialist, 1960 East-West Rd., Honolulu, HI 96822. (808) 947-8573.

March 15-18—**Hawaiian Psychiatric Symposium.** Continuing Medical Education, Inc. at Sheraton-Waikiki. Thursday-Saturday. 25 hrs. $295. Contact: CME, Inc., 2030 E 4th St., Santa Ana 92705. (714) 547-5186.

March 23-25—**General Psychiatry Board Review Course.** UCSF. Friday-Sunday.

March 29-30—**1984 Updates: Medical and Behavioral Treatment.** See Of Interest To All Physicians, March 29-30.

April 28-29—**The Cutting Edge—1984: The Psychotherapy of Borderline and Narcissistic Disorders.** UCSD at Hotel del Coronado, San Diego. Saturday-Sunday. 13 hrs. $250.

May 3-6—**28th Annual Meeting of the American Academy of Psychoanalysis** at Hyatt Regency Hotel, Los Angeles. Thursday-Sunday. Contact: AAP, 30 E. 40th St., Ste. 608, New York, NY 10016. (212) 697-4105.

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** UCD at Holiday Inn Holidome, Sacramento. Thursday-Friday.

May 19-20—**Freud-Jung Symposium: Clinical Issues.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday.

June 8—**8th Annual Psychiatry Symposium.** Southern California Kaiser-Permanente Medical Group at Newport Beach Marriott Hotel. Friday. 6 hrs. $100. Contact: Dept. of Clinical Services, SCKPMG, 4747 Sunset Blvd., Los Angeles 90027.

August 18-23—**Responsibility Issues in Mental Health.** Southern California Psychiatric Institute at Mauna Kea Beach Hotel, Kauela, HI. Saturday-Thursday. 15 hrs. Contact: Gail Waldron, MD, Program Dir., SCPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

RADIOLOGY AND PATHOLOGY

February 29-March 2—**4th Annual Current Approaches to Radiation Oncology, Biology, and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Sunday.

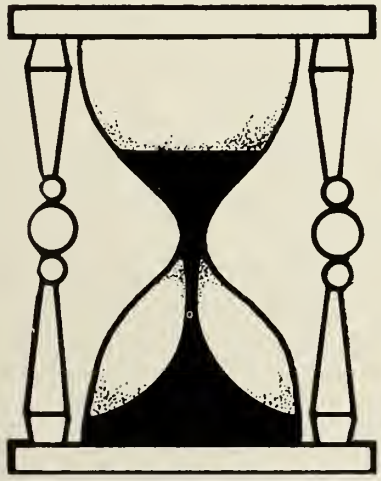
March 3-8—**National Meeting of the American Society of Clinical Pathologists and College of American Pathologists** at Las Vegas. Saturday-Thursday. Contact: ASCP, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-4855.

March 7-9—**5th Annual Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation and the Northern California Radiological Society at Granlibakken Ski and Racquet Resort, Tahoe City. Wednesday-Friday.

(Continued on Page 210)

PRESCRIPTION FOR PREVENTION:

THE CONSEQUENCES OF NUCLEARISM ON AMERICAN MEDICINE AND SOCIETY



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Anaheim Convention Center, Anaheim, California

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University of California, Irvine Extension and the California College of Medicine.

Speakers and Topics

NORMAN COUSINS
Humanity's Quest for Survival in the Nuclear Age

SHEILA TOBIAS
What Kinds of Guns Are They Buying For Your Butter?—An Historical Perspective on the Nuclear Arms Race

B. JACK GEIGER, M.D.
Nuclear Attack: The Medicine and Morality of Civil Defense

SR. CORRINE BAYLEY, M.A.
The Relationship Between the Health Care System and the Arms Race

VICE ADMIRAL JOHN MARSHALL LEE, (U.S.N. RET.)
Thinking About Nuclear Weapons

KENNETH MELMON, M.D.
The Role of the Physician: The Hippocratic Imperative in the Nuclear Age

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The Psychology of War and Peace

GORDON ADAMS, PH.D.
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SP84-234

In clinical anxiety,

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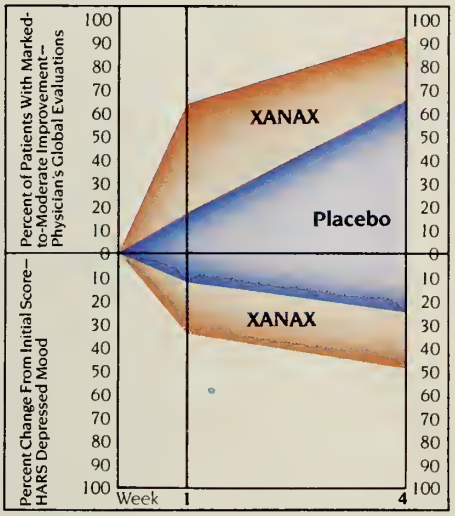
depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

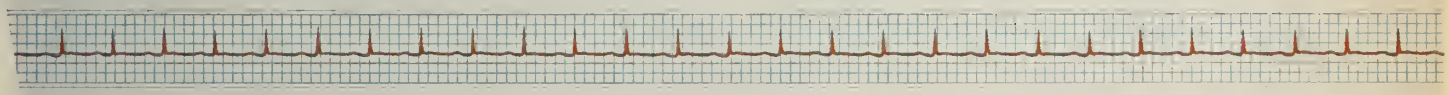
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy



- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file, The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets

alprazolam Ⓒ IV

XANAX® Tablets ©
(alprazolam)

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. BS-1

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Kalamazoo, Michigan 49001 USA

(Continued from Page 206)

18 hrs. $300. Contact: Arthur B. Dublin, MD, Program Dir., SRREF, P.O. Box 19184, Sacramento 95819.

March 12-16—**International Academy of Pathology Annual Meeting.** United States-Canadian Division of the International Academy of Pathology at San Francisco Hilton. Monday-Friday. Contact: Dr. Nathan Kaufman, Sec.-Treas., USCDIAP, 1003 Chafee Ave., Augusta, GA 30904. (404) 724-2973.

March 12-16—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $400.

March 19-21—**New Imaging Technologies.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Monday-Wednesday. Contact: Annenberg Center for Health Sciences-A, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

March 24—**A One-Day Seminar on CT and NMR Imaging of the Spine.** Los Angeles Radiology Society at Westin Bonaventure, Los Angeles. Saturday. 6 hrs. Contact: Richard A. Oas, MD, CT Spine, c/o LARS, 5200 Century Blvd., Ste. 920, Los Angeles 90045.

April 13-15—**B-Scan Ultrasonography Update.** UCSF at Fairmont, San Francisco. Friday-Sunday.

April 13-15—**2nd Annual Seminar Neurodiagnostic Imaging.** UCSF at Meridien Hotel, San Francisco. Friday-Sunday.

April 16-19—**Diagnostic Cytology of the Female Genital Tract.** See Obstetrics and Gynecology, April 16-19.

April 23-27—**Review in Immunohematology and Blood Banking.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 31.5 hrs. Contact: Regional Educational Activities, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-1336, ext. 129.

April 29-May 4—**4th Annual Residents' Radiology Review Course.** UCSD. Sunday-Friday. 37 hrs. $360.

May 7-11—**Clinical Microbiology Update.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 29.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

May 7-11—**San Diego Imaging Symposium.** UCSD. Monday-Friday. 27 hrs. $400.

May 22-25—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Tuesday-Friday. 26 hrs. Contact: R. S. Pakusch, MD, Program Chairman. (415) 561-3764.

June 17-22—**Pathology of the Lung.** UCSD. Sunday-Friday. 50 hrs.

August 14-18—**Radiology Physics Review Course.** UCD at Sacramento. Tuesday-Saturday.

August 20-24—**Radiology of the Abdomen.** UCSD at San Diego and Anaheim. Monday-Friday. 27 hrs. $395.

SPORTS MEDICINE

March 12-16—**University of Hawaii Sports Medicine Course** at Princess Kaiulani Hotel, Waikiki, Honolulu, HI. Monday-Friday. $280. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu, HI 96822. (808) 948-8244.

May 2-6—**Mountain Medicine: 1984.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Tuesday.

May 23-26—**American College of Sports Medicine Meeting** at Town and Country Hotel, San Diego. Monday-Thursday. Contact: T. Miller, Exec. Dir., ACSM, 1440 Monroe St., Madison, WI 53706.

June 14-16—**Knee Problems in Athletes.** American Academy of Orthopaedic Surgeons at Monterey. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

(Continued on Page 212)

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(Continued from Page 210)

June 24-27—**Marine Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Wednesday.

July 20-22—**Sports Medicine and Cardiovascular Fitness—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 23-26—**10th Annual Meeting of American Orthopaedic Society for Sports Medicine** at Marriott Hotel, Anaheim. Monday-Thursday. Contact: AOSSM, P.O. Box 94274, Chicago 60690.

SURGERY

February 15-17—**Urolithiasis Update 1984.** American Urological Association at Meridien Hotel, San Francisco. Wednesday-Friday. 17 hrs. Contact: Alice Henderson, Office of Ed., AUA, P.O. Box 25147, Houston, TX 77265. (713) 799-6070.

February 21-23—**Common Operative Problems in Children's Orthopaedics.** American Academy of Orthopaedic Surgeons at Santa Monica. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

February 23-26—**Federation of Western Societies of Neurological Science—Annual Meeting** at Silverado Country Club, Napa. Wednesday-Saturday. Contact: Program Chairman, Franklin C. Wagner, Jr, MD, Dept. of Neurological Surgery, University of California, Davis Medical Center, 4301 X St., Sacramento 95817.

February 27-March 2—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

March 5-9—**Surgical Forum.** Society of Graduate Surgeons of the Los Angeles County and USC Medical Center at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. Contact: Dir. of Med. Ed., Soc. of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 9-11—**Pathophysiology and Techniques of Cardiopulmonary Bypass IV.** Cardiothoracic Research and Education Foundation and UCSD at Sheraton Harbor Island East, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (619) 272-3126.

March 10-11—**California Association of Neurological Surgeons Meeting** at Pasadena. Saturday-Sunday.

March 16-17—**Advances in External Skeletal Fixation.** UCSF at Hyatt Lake Tahoe, Incline Village. Friday-Saturday. 13 hrs. $250.

March 18-21—**25th Annual Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday. 32 hrs.

March 19-23—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

March 22-24—**The Cutting Edge.** UCSF. Thursday-Saturday.

March 23-25—**Gynecologic Surgery with Emphasis on Gynecologic Urology.** See Obstetrics and Gynecology, March 23-25.

March 24—**Reflections on Cardiac Surgery.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Saturday. 2 hrs. Contact: Heart Institute of the Desert, Wright Bldg., Ste. 406, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

March 24-25—**Avoiding the Pitfalls of Pediatric Office Orthopedics.** See Pediatrics, March 24-25.

March 24-28—**Current Orthopaedic Practice and Surgery.** American Academy of Orthopaedic Surgeons at San Francisco. Saturday-Wednesday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

March 25-28—**21st Annual UCLA Seminar on Controversial Areas in Surgery.** UCLA at Hilton Riviera Hotel, Palm Springs. Sunday-Wednesday. 14 hrs. $410.

March 26-30—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

March 28-April 1—**12th Annual Symposium on Vascular Surgery.** UCLA at Hotel Riviera, Palm Springs. Wednesday-Sunday. 16.5 hrs. $465.

March 29-April 1—**6th National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society of Dermatologic Surgeons at Rancho Las Palmas Resort, Palm Springs. Thursday-Sunday. 16 hrs. Contact: Richard W. Fleming, MD or Toby G. Mayer, MD, 9730 Wilshire Blvd., Beverly Hills 90212.

April 1—**Facial Aesthetic Surgery.** UCSF at Hilton, San Francisco. Sunday.

April 1-5—**12th Annual Spring Meeting American College of Surgeons** at Hilton Hawaiian Village Hotel, Westin Ilikai Hotel. Sunday-Thursday. Contact: ACS, 55 E. Erie St., Chicago 60611.

April 7-14—**Temporal Bone Surgical Dissection—1984.** House Ear Institute, Los Angeles. One week. 62 hrs. $850. Contact: Antonio de la Cruz, MD, Director of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

April 9-13—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

April 12—**Postgraduate Course in General Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday. 15 hrs. $250.

April 12-14—**Endourology.** American Urological Association at Disneyland Hotel, Anaheim. Thursday-Saturday. 18 hrs. Contact: Alice Henderson, Office of Ed., AUA, P.O. Box 25147, Houston, TX 77265. (713) 799-6070.

April 12-14—**Postgraduate Course in General Surgery.** UCSF at Fairmont, San Francisco. Tuesday-Thursday.

April 13-14—**Prosthetic Ligament Reconstruction of the Knee.** UCLA at Century Plaza Hotel, Los Angeles. Friday-Saturday. 12 hrs. $275.

April 19-21—**Nasal Plastic and Reconstructive Surgery.** Pacific Medical Center, San Francisco. Thursday-Saturday. 15 hrs. $350. Contact: Div. of Ed., Presbyterian Hospital of Pacific Medical Center, P.O. Box 7999, San Francisco 94120.

April 28—**50,000 Open-Heart Operations.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Saturday. 2 hrs. Contact: Heart Institute of the Desert, Wright Bldg., Ste. 406, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

May 3-5—**The Wrist.** American Academy of Orthopaedic Surgeons at Newport Beach. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

May 6-9—**American Association of Plastic Surgeons Meeting** at Hotel del Coronado, Coronado. Sunday-Wednesday. Contact: AAPS, Div. of Plastic Surgery, School of Medicine, Univ. of No. Carolina, Chapel Hill, NC 27514. (919) 966-3080.

May 9—**Surgery.** LLU. Wednesday. 4 hrs $50.

May 12—**Cardiac Surgery Research.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Saturday. 2 hrs. Contact: Heart Institute of the Desert, Wright Bldg., Ste. 406, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

May 13-25—**Temporal Bone Surgical Dissection 1984.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

May 21-25—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 1-3—**Failed Arthroplasty Revision and Salvage.** American Academy of Orthopaedic Surgeons at San Francisco. Friday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

June 9-14—**Fingers to the Toes: An Orthopedic Approach for**

(Continued on Page 214)

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CONTACT: _____

(Continued from Page 212)

the Family Physician. UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Saturday-Thursday.

June 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 20-24—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Regency, Maui. Wednesday-Sunday. Contact: WTSA, 13 Elm St., Manchester. MA 01944. (617) 927-8330.

June 21-23—**Gynecologic Surgery: Principles and Techniques.** American College of Obstetrics and Gynecology at Silverado, Napa. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

June 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

OF INTEREST TO ALL PHYSICIANS

February 18-22—**The Doctor's Dilemma: The Delicate Balance Between Humanity and Technology.** Human Dimensions In Medical Education at La Jolla. Saturday-Wednesday. 32 hrs. $400. Contact: Ms. Orienne Strode, Director, HDME, 1125 Torrey Pines Rd., La Jolla 92037. (619) 459-3861.

February 19-22—**4th Annual Conference on Alcoholism and Chemical Dependency Problem Sharing/Solving in Chemical Dependency.** Annenberg Center for Health Sciences of the Eisenhower Medical Center, Rancho Mirage. Sunday-Wednesday. Contact: Annenberg Center for Health Sciences —A, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

February 23-24—**American College of Physicians 1984 Regional Meeting** at Ala Moana Hotel, Honolulu, HI. Thursday-Friday. Contact: Robert A. Nordyke, FACP, 2013 Kakela Dr., Honolulu, HI 96822.

February 23-26—**Hypnosis Training Workshop.** UCI and Southern California Society of Clinical Hypnosis at Grand Hotel, Anaheim. Thursday-Sunday. 28 hrs. Contact: SCSCH, P.O. Box 5835, Sherman Oaks 91403. (213) 872-3350.

March 2-3—**American College of Physicians 1984 Regional Meeting** at Holiday Inn, Napa. Friday-Saturday. Contact: Jerry P. Lewis, FACP, 618 Francisco Place, Davis 95616.

March 7-9—**34th Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Continuing Ed., Mt. Zion Hospital, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

March 10—**Prescription for Prevention: The Consequences of Nuclearism on American Medicine and Society.** UCI at Anaheim Convention Center. Saturday. 6 hrs. $60.

March 14-17—**Contemporary Obstetrics: A Guide to the Physician in Practice.** See Obstetrics and Gynecology, March 14-17.

March 16-18—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel del Coronado, Coronado. Friday-Sunday. 20 hrs. $250. Contact: Jackie Shiller, Continuing Medical Education Associates, P.O. Box 84296, San Diego 92138. (619) 223-2997.

March 22-24—**Postgraduate Institute.** California Medical Association at Yosemite. Thursday-Saturday.

March 24—**Alcoholism: 1984.** UCD at Red Lion Motor Inn, Sacramento. Saturday.

March 25-28—**Nutrition Conference.** UCSF at Yosemite. Sunday-Wednesday.

March 26-30—**Family Medicine Board Review Course.** UCSD at Palm Springs. Monday-Friday.

March 29-30—**1984 Updates: Medical and Behavioral Treatment.** Scripps Clinic and Research Foundation, La Jolla. Thursday-Friday. Contact: Dianne Tisue, Conference Coordinator, Scripps Clinic and Research Fndn, 10666 N. Torrey Rd., La Jolla 92037. (714) 455-9100.

April 1-4—**Dermatology for the Clinician.** UCD at Yosemite. Sunday-Wednesday.

April 4-8—**Wound Management.** UCSD at San Diego Hilton Hotel. Wednesday-Sunday.

April 6—**Laboratory Aids in Clinical Diagnosis.** LLU at Casa Royale Motor Inn, Bakersfield. Friday. 6 hrs. $75.

April 6-8—**Sexual Issues in Medical Practice.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. 14 hrs.

April 25-26—**Research in Continuing Medical Education.** UCSF. Wednesday-Thursday.

May 5-12—**Challenges in Acute Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Poplin Creek Estate, Ojai. One week. Contact: Richard F. Paris, MD. (208) 788-4995.

May 14-18—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

May 18-20—**The Primary Care Physician and Cancer.** See Cancer, May 18-20.

May 19-20—**12th Annual Family Practice Symposium.** Southern California Permanente Medical Group at Sheraton Universal Hotel, North Hollywood. Saturday-Sunday. 11 hrs. Contact: SCPMG, Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

May 20-24—**Family Practice Refresher Course.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Thursday.

May 29-June 2—**11th Annual UCLA Santa Monica Hospital Medical Center Family Practice Refresher Program.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Tuesday-Saturday. 35.5 hrs. $385.

June 1-12—**Southwestern Regional Cutancous Flap Workshop.** Dermatology Research Foundation of California at UCLA. Friday-Saturday. 14 hrs. $495. Contact: Daniel E. Gormley, MD, 412 W. Carroll, Ste. 207, Glendora 91740.

June 5-8—**Society of Nuclear Medicine 31st Annual Meeting** at Los Angeles Convention Center. Tuesday-Friday. 36 hrs. Contact: Meetings Dept., SNM, 475 Park Ave. So., New York, NY 10016. (212) 889-0717.

June 8—**Occupational Medicine.** UCD at Beverly Garland Motor Lodge, Sacramento. Friday.

June 11-15—**Review in Clinical Chemistry.** American Society of Clinical Pathologists at Monterey. Monday-Friday. 35 hrs. Contact: Reg. Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

June 14-16—**Postgraduate Institute—Geriatrics.** CMA at Hyatt, Lake Tahoe. Thursday-Saturday.

June 17-23—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center of Long Beach at Grand Hotel, Anaheim. One week. Contact: MMCLB, 2801 Atlantic Ave., Long Beach 90801. (714) 595-3811.

June 20-24—**Golden State Medical Association Annual Scientific Session** at Hawaiian Regent Hotel, Oahu. Wednesday-Sunday. Contact: Lillian Fortier, GMSA, P.O. Box 2151 Station A, Berkeley 94702.

June 21-23—**1st Annual Superficial Anatomy and Cutaneous Surgery for Dermatologists: 1984.** UCSD. Thursday-Saturday. 22.5 hrs. $500.

July 7-8—**Weekend with the Masters.** UCSD and Great Teachers Foundation at Double Tree Inn, Monterey. Saturday-Sunday. 20 hrs. $325. Contact: P.O. Box 61203, DFW Airport, TX 75261. (214) 659-4590.

(Continued on Page 323)

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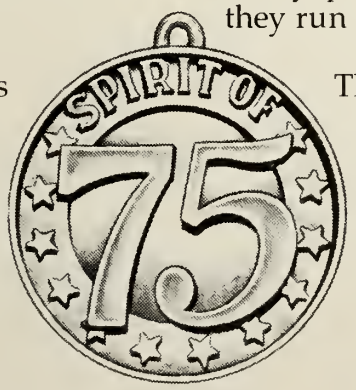

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations, particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]. Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene and leukopenia, thrombocytopenia, agranulocytosis and aplastic and hemolytic anemia have been reported with thiazide. Thiazide may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide. Dosage adjustment may be necessary. Clinically insignificant reductions in intestinal responsiveness to tubocurarine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in patients with impaired renal function. Antihypertensive effects may be enhanced in postsympathectomy patients. Dyazide has been found in [illegible] patients with [illegible] cirrhosis. Therefore Dyazide should be used with caution in patients with hepatic cirrhosis or ascites. Anuria has occurred in patients with renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore it is not advised to administer indomethacin and Dyazide. Interactions of other agents with Dyazide: The following may [illegible] elevated BUN or creatinine: [illegible] diabetic insulin requirements may be altered. Hyperuricemia and gout: digitalis toxicity at [illegible] hypokalemia; digitalis glycosides are very sensitive to potassium depletion. Dyazide interferes with fluorescent measurement of quinidine. Hyperkalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as diuretic hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

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Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

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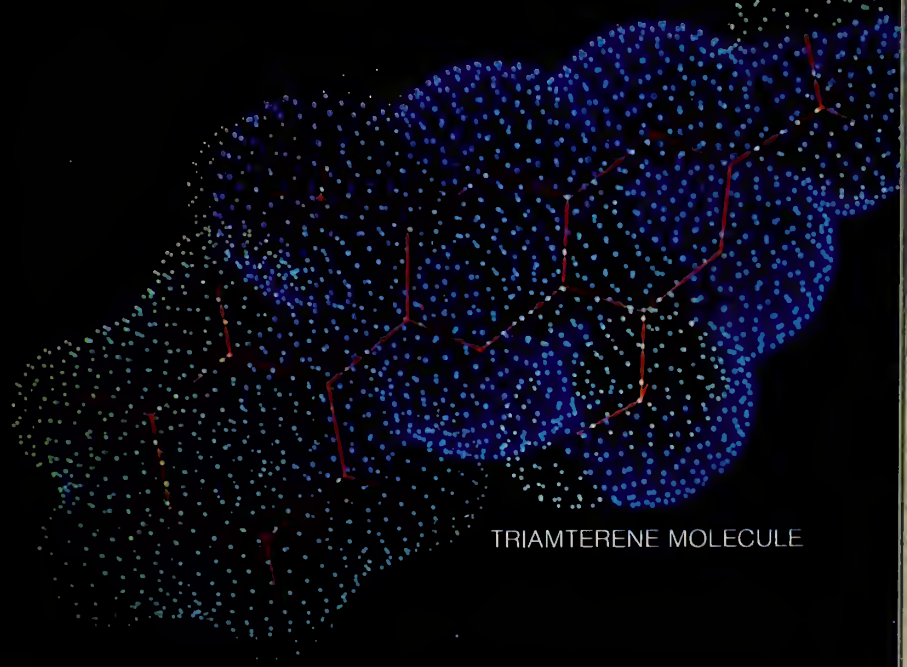

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Clinical Investigation

Antibiotic-Associated Colitis

ANDY STERGACHIS, PhD; DAVID R. PERERA, MD, *and* MARGARET M. SCHNELL, RRA, *Seattle, and* HERSHEL JICK, MD, *Waltham, Massachusetts*

We determined the incidence of antibiotic-associated colitis among users of oral antibiotics or topical clindamycin in a large prepaid health plan. Exposure to antibiotics was determined using a system that automatically records outpatient prescriptions filled and hospital diagnoses were available from computer files. Four cases of acute colitis were judged likely to be causally linked with outpatient use of antibiotics. These findings provide substantial evidence that antibiotic-associated colitis requiring hospital treatment occurs very rarely.

(Stergachis A, Perera DR, Schnell MM, et al: Antibiotic-associated colitis [Clinical Investigation]. West J Med 1984 Feb; 140:217-219.)

Certain drugs have been implicated in the development of colitis. Most notably, pseudomembranous colitis has been reported after systemic therapy with lincomycin, clindamycin hydrochloride, ampicillin, erythromycin ethylsuccinate, tetracycline hydrochloride and cephalosporins.[1-4] Recently, several cases of pseudomembranous colitis after topical application of clindamycin hydrochloride for acne vulgaris were reported.[5,6] We report on the relationship of orally given antibiotics and topical clindamycin used in the outpatient setting and newly diagnosed colitis leading to admission to hospital. The study encompassed a large, defined outpatient population and their hospital experience.

Patients and Methods

The Group Health Cooperative of Puget Sound is a consumer-owned cooperative founded in Seattle in 1947. As of January 1, 1980, there were about 280,000 members. The plan provides comprehensive prepaid medical coverage for outpatient care, drugs and hospital services. The vast majority of drugs are provided free of charge for most of the membership and at a reduced cost for the rest. With few exceptions, members are admitted to hospitals in the Seattle area maintained by the Cooperative.

Information on all discharges from Group Health hospitals has been recorded and placed on computer files by the Commission on Professional and Hospital Activities-Professional Activity Study (CPHA-PAS) in Ann Arbor, Michigan, since 1972. This information includes hospital discharge diagnoses and the surgical procedures done, together with routine demographic data. These records provide ready identification of persons with colitis-related disorders.

In July 1975 the Cooperative began to computerize records of all prescriptions filled in its regional outpatient pharmacies. This process was accomplished in stages by phasing in one regional pharmacy at a time, and was completed by July 1, 1976. Of some 500 women interviewed in previous studies of this population, 98% stated that they routinely used the Group Health pharmacies to fill their prescriptions.[7] Also, among 387 persons interviewed in a recent study, it was reported that 90% of their prescriptions were obtained from Group Health pharmacies. Thus, the outpatient drug-use records, including dates, of virtually all members are accessible in machine-readable form and can be readily linked to hospital care information. The availability of detailed information on drug use in a defined population enabled us to calculate the incidence of colitis among those who received drugs of interest.

From the CPHA-PAS files we identified 344 persons with a hospital discharge diagnosis of colitis (Hospital-International Classification of Diseases Adapted [H-ICDA] codes 563, 563.1, 563.2, 563.9, 564.1, 564.9)

From the Group Health Cooperative of Puget Sound, Seattle, and the Boston Collaborative Drug Surveillance Program, Boston University Medical Center, Waltham, Massachusetts.

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Reprint requests to Hershel Jick, MD, Boston Collaborative Drug Surveillance Program, 400-1 Totten Pond Road, Waltham, MA 02154.

between 1977 and 1980. Excluded from further study were eight persons who had been members of the Group Health Cooperative for less than six months because the history of recent drug use and past history were insufficient. Also excluded from further evaluation were 120 persons in whom colitis was a secondary diagnosis unrelated to the primary reason for admission to hospital. An additional 115 persons were excluded because the record indicated that they had had chronic colitis before the admission under study. Patients who had chronic colitis were defined as those with previous admissions for colitis or those receiving sulfasalazine before the admission.

There remained 101 persons admitted to the hospital for the first time (according to our records) for acute colitis. For these patients, the entire clinical record was sought and reviewed to determine the reason for the admission to hospital.

Four medical records could not be found. In addition, 90 more cases were excluded from the study because the medical records showed a diagnosis or other evidence of Crohn's disease, functional bowel disorders or chronic colitis. There remained 11 patients admitted to hospital for the first time for acute colitis.

Results

Four of the 11 patients with acute colitis had received antibiotics by mouth as outpatients just before symptoms developed. The other seven cases did not receive antibiotic therapy within three months of symptoms developing. Details of each of the four cases are given below.

Reports of Cases

CASE 1. The patient, a 34-year-old woman with no past history of colitis, was started on a regimen of dicloxacillin sodium, 1 gram a day, for a toe infection. She had severe lower abdominal pain and crampy pain a week after starting the therapy. She was subsequently admitted to hospital after three weeks of crampy lower abdominal pain. During the hospital stay, sigmoidoscopy showed unusual colitis with patches of adherent whitish plaques. Rectal biopsy findings were typical of pseudomembranous colitis. The discharge diagnosis was pseudomembranous colitis due to dicloxacillin administration. She was given a course of vancomycin and no further colitis-related problems were reported during the following period.

CASE 2. The patient was a 38-year-old man with no previous history of colitis. Ampicillin was prescribed, 2 grams a day for seven days, for acute epididymitis. Two days after starting the ampicillin regimen, he had abdominal cramping and loose stools with some blood mixed in them. He was admitted to hospital five days after onset of the abdominal symptoms. The patient had a normal leukocyte count and was afebrile on admission. Laboratory investigation during the hospital course showed no ova, parasites, *Shigella* or *Salmonella* in the stool cultures. Sigmoidoscopy showed that the sigmoid mucosa was somewhat granular and red but not bleeding. The patient's bloody diarrhea stopped after admission and he was discharged with a diagnosis of possible antibiotic-induced colitis. There were no further colitis episodes during the follow-up period.

TABLE 1.—*Rate of Cases of Antibiotic-Associated Colitis at Group Health Cooperative of Puget Sound (Seattle), 1977-1980*

Antibiotic	*Persons Receiving Drug Number*	*Cases of Colitis Among Users Number*	*Rate Per 100,000 Persons*
Dicloxacillin sodium	34,315	1	2.9
Tetracycline hydrochloride	72,684	2	2.6
Ampicillin	63,518	1	1.6
Penicillin	97,255	0	0
Erythromycin ethylsuccinate	77,857	0	0
Amoxicillin trihydrate	18,883	0	0
Cephradine	10,569	0	0
Clindamycin hydrochloride	1,509	0	0

CASE 3. The patient, a 34-year-old man, was prescribed a ten-day course of tetracycline, 1 gram per day, for prostatitis. Two weeks later he was given a ten-day course of ampicillin, 1 gram per day, for the same condition. He was admitted to hospital 11 days after starting the ampicillin regimen because of severe crampy lower abdominal pain for ten days. Sigmoidoscopy showed a purulent mucoid exudate coating the wall of the colon and a moderately severe colitis with irregular patchy ulceration. The rectal biopsy specimen showed nonspecific acute and chronic inflammation. Examination of stool specimens was negative for ova and parasites and cultures showed no enteric pathogens. The discharge diagnosis was colitis. Sigmoidoscopy two months after discharge showed that the colitis had completely resolved.

CASE 4. The patient, a 21-year-old previously healthy woman, was admitted to hospital with a history of bloody diarrhea for five weeks. One week before the onset of symptoms she was placed on a 25-day regimen of tetracycline, 500 mg a day, and benzoyl peroxide for acne. Sigmoidoscopy done during the hospital course showed a number of shallow ulcerative lesions in the rectal ampulla, more severe distally. The discharge diagnosis was ulcerative colitis. The colitis was quiescent during the follow-up period.

The four antibiotics implicated in the cases reported above and other antibiotics not implicated are shown in Table 1. The estimated incidence of admission to hospital of cases of antibiotic-associated colitis among users of oral ampicillin, dicloxacillin and tetracycline was 1.6, 2.9 and 2.6 per 100,000 persons exposed, respectively. There were no cases of colitis among the 1,509 persons receiving clindamycin topically or orally.

Discussion

These findings provide substantial evidence that antibiotic-associated colitis requiring hospital treatment occurs very rarely. Only four cases of colitis were judged to be linked with antibiotic use in a population of some

280,000 persons over a four-year period, despite the fact that outpatient antibiotic use in this population was common. Interestingly, two cases were not treated either because the attending physician did not know of the previous antibiotic therapy or because the patient improved with symptomatic treatment. Each of the drugs implicated (ampicillin, doxycycline and tetracycline) has been previously linked to colitis.[1-4] Until now, however, there have been no reported estimates of the incidence of antibiotic-associated colitis in a well-defined population using antibiotics orally or topically as outpatients.

None of the cases of colitis involved topical forms of clindamycin or erythromycin. During the study period, the Group Health Cooperative compounded a 1.2% topical preparation from clindamycin hydrochloride capsules. A total of 1,509 persons received oral or topical clindamycin prescriptions during the study period. Using pharmacy records, we estimated that about 1,124 prescriptions were for the topical form during the study period. The experience with topical clindamycin in the present study at the Group Health Cooperative is too small to rule out a rare instance of colitis from this preparation. However, the data are sufficient to rule out the possibility that this complication is common (lincomycin was not used by this population). About 5.3% of the erythromycin used was in the topical form. All other antibiotics reported in this study were given orally.

The information presented is free of major selection biases because all diagnosed cases of acute colitis in a defined population were identified from preexisting computer files. In addition, recall bias for drug use is avoided by using automated recording of prescriptions refilled and review of the clinical record.

Mild cases of antibiotic-associated colitis that did not require hospital treatment would not be found by our methods. Also, patients who had antibiotic-associated diarrhea without colitis may have been missed. *Clostridium difficile* toxin assays were not routinely available at the time of this study.

The generally reassuring findings reported here do not reduce the need for caution in the outpatient use of antibiotics. All patients receiving antibiotics should be warned to consult their physicians if diarrhea or other intestinal symptoms occur.

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Lack of Association of Diagonal Earlobe Crease With Other Cardiovascular Risk Factors

LYNN B. JORDE, PhD; ROGER R. WILLIAMS, MD, *and* STEVEN C. HUNT, PhD, *Salt Lake City*

The relationship between diagonal earlobe crease and coronary risk factors, controlling for age and sex effects, was tested in 686 persons. A positive correlation ($\rho = .86$, $P < .001$) is obtained between age and percentage of persons with earlobe creases in each one-year age interval; no sex difference is seen. To test for associations between cardiovascular risk factors and earlobe creases, 67 persons with creases are compared with 67 controls (matched by age and sex) without creases, using the following variables: diastolic and systolic blood pressures, cigarette smoking, weight, height, scapular skinfold thickness, serum cholesterol level, high-density lipoprotein level, intracellular sodium, sodium-lithium countertransport, plasma renin level and the presence of diabetes and hypertension. None of these variables differs significantly between cases and controls, indicating that the previously documented association between earlobe crease and coronary heart disease may be independent of these risk factors. Although coronary heart disease has often been shown to aggregate in families, no familial aggregation is found for earlobe creases.

(Jorde LB, Williams RR, Hunt SC: Lack of association of diagonal earlobe crease with other cardiovascular risk factors [Clinical Investigation]. West J Med 1984 Feb; 140: 220-223.)

A number of studies have shown a significant association between coronary heart disease and the presence of diagonal earlobe creases.[1-4] It is unclear whether this association is independent of other coronary risk factors or due to a mutual association of coronary risk factors with both coronary heart disease and earlobe creases. For example, in several studies a positive association was found between creases and hypertension,[4-7] while in others none was found.[2,3] In all but one of these studies[7] only patients with disease were selected (usually those who had had a myocardial infarction). This selection process could easily introduce biases and confounding effects in an evaluation of the association between risk factors and earlobe creases. In addition, most previous efforts have surveyed a limited number of risk factors.

We report findings on a group of persons who were not themselves selected because of a history of coronary heart disease. A large number of risk factors have been evaluated for their association with earlobe creases, several of which have not been considered in previous studies. Also, because coronary heart disease has often been observed to cluster in families, sib-sib aggregation of earlobe creases was measured.

Subjects, Data and Methods

Study subjects included 286 persons younger than age 20 years and 400 adults aged 20 years or older, equally divided between male and female subjects. They are members of pedigrees prone to hypertension, stroke or early coronary artery disease—that is, most of the adults had parents or grandparents with early coronary

From the Departments of Human Genetics (Dr Jorde) and Medicine (Drs Williams and Hunt), University of Utah School of Medicine, Salt Lake City.
Submitted, revised, October 24, 1983.
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Reprint requests to Lynn B. Jorde, PhD, Dept of Human Genetics, University of Utah School of Medicine, 50 North Medical Dr, Salt Lake City, UT 84132.

TABLE 1.—*Prevalence of Earlobe Creases By Age and Sex*

Age Interval	Sample Size ♂	Sample Size ♀	Crease on Either or Both Ears (%) ♂	Crease on Either or Both Ears (%) ♀
0-9	53	68	1.9	0.0
10-19	91	74	0.0	0.0
20-29	61	68	3.3	1.5
30-39	43	55	16.3	7.3
40-49	37	26	27.0	34.6
50-59	37	34	64.9	61.8
60-69	13	13	76.9	61.5
≥70	5	8	80.0	100.0
TOTAL	340	346	17.1	14.7

artery disease or stroke. Based on their family history of cardiovascular disease, the subjects were asked to participate in the clinical evaluation described below. Most of them were free of cardiovascular disease at the time of their evaluation. Hypertension was present in 68, diabetes in 20 and coronary artery disease manifestations in 10.

All subjects participated in a four-hour screening protocol at the Cardiovascular Genetics Research Clinic, University of Utah. Data collection included personal health and habits history, fasting blood samples, a standard 12-lead electrocardiogram, anthropometrics, 21 blood pressure measurements and physicians' history and physical examination. The presence of earlobe creases was evaluated in all subjects. The creases were identified in standing persons as a diagonal wrinkle extending across a third or more of the earlobe's surface. Sodium-lithium countertransport was determined using a modification of Canessa's method.[8] Plasma cholesterol, high-density lipoprotein and renin levels were assayed using standard clinical chemistry methods at the University of Utah Medical Center.

Familial aggregation of earlobe creases was tested using a subset of 82 adults older than age 30 in 29 sibships. Relative odds for siblings of persons with creases were calculated by adapting Altham's[9] method to deal with related pairs of persons rather than related persons. Essentially, the method consists of creating 2×2 contingency tables that compare presence and absence of creases for pairs of sibs. Older sib pairs tend to be concordant for earlobe creases due to the correlation of age with earlobe creases. To control for age effects, the sib pairs were stratified into several different age groups.

Results

In Table 1 is listed the age and sex distribution of earlobe creases (on either or both ears) in this population. Among the 109 subjects with creases, 77 (70.6%) had creases of both ears. The prevalence of creases increases greatly with age. The product-moment correlation between age and the proportion of persons with creases in each one-year age interval is .866 ($P<.0005$). A rank-order correlation test (Spearman's ρ) gave a similar value: .863 ($P<.001$). The difference between sexes in percent with creases is statistically nonsignificant and shows no consistent pattern across age groups.

In this population it was possible to match (by five-year age interval and sex) 67 persons with creases on either or both earlobes (cases) with an equal number who had no crease on either earlobe (controls). In Table 2 are given the mean values of a number of coronary artery disease and hypertension risk factors for the cases and controls, as well as significance levels for t tests. There was no significant difference between cases and controls for any of these risk factors. Of the 67 cases, 19 (28.4%) had a diagnosis of hypertension, as did 19 of the controls. One (1.5%) of the cases had had a myocardial infarction, whereas three (4.5%) of the controls had had a myocardial infarction. Diabetes had been diagnosed in six (9.0%) of the cases and in four (6.0%) of the controls. Application of a test for the equality of two percentages[10] shows the difference between the latter two pairs of percentages to be nonsignificant. Because of the small numbers involved, however (especially for the cases of myocardial infarction), this result should not be regarded as conclusive.

Eleven of the cases and 17 of the controls were receiving medication for hypertension. The t tests were run on a sample in which these persons were removed.

TABLE 2.—*Mean Values for Coronary Risk Factors in 67 Cases and 67 Controls*

Coronary Risk Factors	Cases Mean	Cases Sample Size	Controls Mean	Controls Sample Size	Significance
Diastolic blood pressure (mm/mercury)*	75.4	67	75.8	67	NS
Systolic blood pressure (mm/mercury)*	114.4	67	115.9	67	NS
Years of cigarette smoking	4.1	67	2.9	67	NS
Weight (kg)	79.9	67	77.7	67	NS
Height (cm)	167.8	67	168.6	67	NS
Scapular skinfold thickness (mm)	267.6	67	252.7	67	NS
Cholesterol (mg/dl)	214.5	66	205.8	67	NS
High-density lipoprotein (mg/dl)	50.6	47	54.2	51	NS
Intracellular sodium (mM)	50.6	67	54.9	67	NS
Sodium-lithium countertransport†	288.0	62	282.1	63	NS
Renin (ng/ml/hour×100)	160.6	65	175.9	65	NS

*Average of six resting sitting measurements.
†μmol an hour per liter of erythrocytes according to a modification of Canessa's[8] method.

The mean values for each risk factor were very similar to those of the full sample, and again no differences were statistically significant.

In the analysis of familial aggregation, 32 of the 82 adults had earlobe creases. Calculation of relative odds (Table 3) shows that the probability of observing an earlobe crease in a person is not statistically raised when the person's sibling has an earlobe crease. As expected, older siblings were usually concordant for the presence of crease, and younger siblings were usually concordant for the absence of crease.

Discussion

While most studies have shown a positive association between earlobe creases and coronary heart disease, at least one showed no association.[11] Because our population was not selected on the basis of disease, the number of cases of myocardial infarction was quite small. However, there were 15 persons who had had a myocardial infarction (average age, 55.5 years). Of these, 11 (73.3%) had earlobe creases. The incidence of creases in the 50- to 59-year-old age group of our clinic population was 63.4%. The difference between these two percentages is not statistically significant ($P>.4$; test for the equality of two percentages). However, the sample size for the myocardial infarction group is small, and the difference of the two percentages is in the expected direction. In another study in the Salt Lake City area, Blodgett[12] compared 77 patients with myocardial infarction and 77 controls (matched for age and sex) for the presence of earlobe creases. The average age in both groups was 61.5 years. Among the infarction cases, 75% had earlobe creases, whereas 35% of the controls had creases. This difference is highly significant. These data and our own both lend further support to the relationship between coronary artery disease and earlobe creases.

It is interesting that while the percentage of creases among Blodgett's cases of myocardial infarction was similar to that of our study, the percentage among the controls was substantially lower. This could reflect the fact that many of the persons in our study population are members of families prone to coronary artery dis-

TABLE 3.—*Frequency of Earlobe Creases in Sibling Pairs*

	Number of Pairs With Crease in			
	Both Persons	*One Person*	*Neither Person*	*Relative Odds**
Both age 50+	22	9	4	1.1
Younger pairs	10	27	82	1.1

*None statistically significant.

TABLE 4.—*Percentages of Ear Creases by Age in This and Other Studies**

Study Age	*Lichstein, et al[3] CHD*	*Lichstein, et al[3] Control*	*Schoenfeld, et al[4] CHD*	*Schoenfeld, et al[4] Control*	*Petrakis and Koo[13] Control*	*Haft, et al[14] CHD*	*Haft, et al[14] Control*	*Christiansen, et al[15] CHD*	*Christiansen, et al[15] Control*	*Rhoads, et al[16] CHD*	*Rhoads, et al[16] Control*	*This Study Control*
0-9 ...	...	...	...	...	...	...	...	...	...	...	...	1
10-19 ...	...	...	...	...	...	...	...	...	...	...	...	0
20-29 ...	...	...	...	...	18	11	0	...	...	...	...	2
30-39 ...	15	14	73	25	23			0	4	...	...	11
40-49 ...	46	39				52	27	0	2	...	...	30
50-59 ...	48	28	80	40	51			47	14	26	30	63
60-69 ...	55	40	74	38		63	53	43	24	28	35	69
≥70 ...	45	37	83	44				47	35	42	26	92

CHD = coronary heart disease

*Brackets indicate different grouping of ages.

TABLE 5.—*Summary of Relationships Between Earlobe Creases and Coronary Risk Factors From Other Studies*

Study	*Hypertension*	*Diabetes*	*Smoking*	*Obesity*	*Cholesterol*	*HDL*	*Triglyceride*
Kaukola, et al[2]	0	0	0	0	0	0	0
Lichstein, et al[3]	0	0	0	...	...	...	...
Schoenfeld, et al[4]	1	...	0	...	0	...	...
Kristensen[6]	1	...	...	...	...	...	...
Moncada, et al[7]	1	0	...	...	0	...	0
Haft, et al[14]	0	...	0	1	0	...	0
This study	0	0	0	0	0	0	...

HDL = high-density lipoprotein

*1 = significant association found, 0 = no association found, ... = no information.

ease and may thus present ear creases as an early sign of a predisposition to coronary disease. However, the lack of familial aggregation of ear creases noted above militates somewhat against this conjecture.

A positive correlation between age and ear creases has been observed in most other studies,[1-3,11-15] but at least two studies[4,16] failed to show this relationship. In addition, as Table 4 shows, the percentages of creases in each age class varies widely from study to study. These inconsistencies may reflect differences in sampling procedures—that is, differences among patients with myocardial infarction, hospital patients in general and healthy persons—methods of diagnosing earlobe creases, age intervals sampled (only older men were sampled in one study[16]) and ethnic composition of the study populations.[13] Our study population is comprised mostly of persons of northern European descent, and our distribution of creases by age corresponds fairly well with that obtained by Petrakis and Koo[13] for their "white" population sample. Generally, however, the frequencies in our study population tend to be higher than those of the controls from other populations. Again, this may reflect the ascertainment factor mentioned above.

The lack of a sex difference in earlobe crease prevalence is consistent with the findings of two other studies,[4,17] though one other survey found a significant difference.[14] In our study, it is especially interesting that premenopausal women, who have lower rates of myocardial infarction than men of comparable ages, do not show lower percentages of earlobe creases.

The relationships found between creases and coronary risk factors in other studies are summarized in Table 5. The study of Frank[5] was not included in this table because it did not use a control population. The table indicates that most risk factors are not associated with ear creases, a finding that agrees with the results of our study. Three studies did show an association with hypertension, however, whereas ours did not. (It should be noted that Rhoads and co-workers[16] found a small but significant difference in systolic blood pressure but no difference in diastolic pressure.) In one of these studies,[4] the comparison for earlobe creases was done only on patients who had had a myocardial infarction; this could well account for their result. The study most comparable to ours is that of Moncada and associates[7] because they studied healthy persons. They did find a positive association between hypertension and earlobe creases. These conflicting results could be due to different sampling schemes (we sampled families at risk for hypertension) or the dissimilar ethnic backgrounds of the two populations, or both.

A frequently voiced concern is that the earlobe crease may be associated with coronary heart disease because of a mutual association with some other coronary risk factor.[3] Our results indicate that earlobe creases are not associated with another major risk factor and may therefore be an independent diagnostic sign for coronary heart disease.

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Cefonicid as Therapy for Uncomplicated Gonococcal Urethritis Caused by Penicillinase-Producing *Neisseria gonorrhoeae*

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Young men with uncomplicated gonococcal urethritis were treated with 1 gram of cefonicid given intramuscularly plus 1 gram of probenecid by mouth. Of 53 evaluable patients, 33 (62%) had penicillinase-producing Neisseria gonorrhoeae. *All but one of these patients were cured. All men who had penicillin-sensitive infections were cured. Cefonicid was highly effective in the treatment of both penicillin-sensitive and penicillin-resistant* N gonorrhoeae. *Other than moderate pain at the site of injection, there were no adverse side effects. Cefonicid can be added to the group of newer cephalosporins that are effective in the treatment of gonococcal urethritis caused by either penicillin-sensitive or penicillin-resistant strains.*

(Sanchez PL, Lancaster DJ, Berg SW, et al: Cefonicid as therapy for uncomplicated gonococcal urethritis caused by penicillinase-producing *Neisseria gonorrhoeae* [Clinical Investigation]. West J Med 1984 Feb; 140:224-226.)

Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) have been occurring since 1976,[1,2] and the incidence of these infections has increased significantly since 1980.[3] In some parts of the western Pacific, the proportion of all cases of gonorrhea caused by PPNG is as high as 65%.[4] Several cases of PPNG also resistant to spectinomycin have recently been reported.[5,6] Because of these findings, a clinical evaluation of intramuscular cefonicid therapy plus 1 gram of probenecid given by mouth for gonococcal urethritis was undertaken. Cefonicid has been shown to have a broad range of activity against both Gram-positive and Gram-negative organisms including *N gonorrhoeae,* and it has shown activity against several types of β-lactamases.[7] It was chosen for this evaluation because of these attributes.

Patients and Methods

The study was conducted among US military personnel stationed at Subic Bay, Republic of the Philippines. The study population was comprised of male active duty Navy and Marine Corps personnel, 18 years of age and older, who had presented to sick call with signs and symptoms of uncomplicated gonococcal urethritis. All subjects agreed voluntarily to participate in the study and signed a statement of informed consent. Subjects were enrolled if all the following criteria were met: recent sexual exposure, signs or symptoms of urethritis, and a urethral Gram stain that was positive for polymorphonuclear leukocytes and intracellular Gram-negative diplococci. Patients were excluded from the study if they had a complicated gonococcal

From the Infectious Diseases Division, Department of Internal Medicine, and the Clinical Investigation Department, Naval Hospital, San Diego. This article is considered, under the Copyrights Act, a "work of the United States government" and accordingly there is no copyright. The opinions or assertions expressed are those of the authors and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or the naval service at large.

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TABLE 1.—*Cumulative Percent of Penicillin-Sensitive and Penicillin-Resistant* Neisseria gonorrhoeae *Isolates Susceptible to Increasing Concentrations of Cefonicid and Penicillin*

	Penicillin-resistant Isolates (n = 46)		*Penicillin-sensitive Isolates (n = 35)*	
μg/ml	*Cefonicid*	*Penicillin*	*Cefonicid*	*Penicillin*
0.04	7	...	6	...
0.08	7	...	6	...
0.16	9	...	6	...
0.31	15	...	9	69
0.62	15	...	14	80
1.25	15	...	14	86
2.50	59	...	66	95
5.00	100	13	100	98
10.00	...	15	...	100
20.00	...	26	...	...
>20.00	...	100	...	...

TABLE 2.—*Gonococcal Urethritis: Cure Rate Using Cefonicid*

	Cefonicid 1 Gram		
Gonococcal Strain	*Number Treated*	*Number Cured*	*(% Cured)*
Penicillinase-positive	33	32	(97)
Penicillinase-negative	20	20	(100)
TOTAL	53	52	(98)

infection, coexisting syphilis, were taking other antibiotics or had a history of serious allergic reaction to penicillin, cephalosporins or probenecid.

Diagnostic specimens were obtained by inserting a calcium alginate swab 2 to 4 cm into the urethra, followed by immediate inoculation directly onto modified Thayer-Martin media and incubation at 35.5°C in an incubator with 5% carbon dioxide concentration. Gram stains of urethral smears were read by an experienced laboratory technologist or by one of the investigators.

After the patients had been examined and urethral specimens obtained, each was given a 1-gram dose of cefonicid intramuscularly. The drug was given in two divided doses at one session. Just before injection, the subject received 1 gram of probenecid by mouth.[8] All patients were observed for drug intolerance or allergy for 30 minutes after injection.

All urethral cultures were examined after 24 and 48 hours. Based on typical colonial morphology, Gram stain and positive oxidase test, a presumptive identification of *N gonorrhoeae* was made. Colonies were subcultured onto chocolate agar and regrown for β-lactamase determination using the rapid iodometric technique.[9]

Subjects returned two to eight days after therapy for test-of-cure cultures. Each patient was interviewed for adverse drug reactions, intercurrent sexual exposure and clinical course. Urethral cultures were obtained from all subjects, and Gram stains were obtained from those with persistent or recurrent symptoms. Men with evidence of recurrent or persistent gonorrhea were treated immediately with 2 grams of spectinomycin intramuscularly whereas those with evidence of post-gonococcal urethritis (PGU) were given tetracycline.

The bacterial isolates from patients in this study were lost in transit from the Philippines before antibiotic sensitivity testing. Table 1 shows the sensitivity to cefonicid, as done by methods described previously,[10] of gonococcal isolates obtained from patients at the same military facility two months before the cefonicid study. This information provides an approximation of the susceptibility of the gonococci that were treated with cefonicid.

Results

Sixty-two patients were enrolled in the study. Nine were excluded from evaluation because of either negative pretreatment culture for *N gonorrhoeae* or failure to return for follow-up. This left 53 evaluable patients. Among this group there were 52 cures (98%). The one cefonicid failure occurred in a patient who was infected with a β-lactamase-producing strain of gonococcus (Table 2). There were no toxic or adverse effects noted with cefonicid except for pain at the injection site.

Discussion

As predicted from in vitro sensitivity testing[7] and experience with other recently developed cephalosporins,[10-13] cefonicid proved to be very effective in treating uncomplicated gonococcal urethritis in men. The 98% cefonicid cure rate is essentially the same as that achieved with ceftriaxone,[10] cefoxitin[11] or ceftizoxime[13] and is quite acceptable. Cefoxitin has been shown to be highly effective in treating gonococcal arthritis caused by PPNG,[14] but cefonicid has not yet been tested against other than uncomplicated gonococcal urethritis. Thus, until further data are available concerning the efficacy of cefonicid in women, men with anorectal infections and persons with other complicated infections, it should not be routinely used for treating gonorrhea. It would appear that for the present cefonicid should be held in reserve. Development of antibiotic resistance may necessitate substitution of cefonicid for other treatments in the future. Alternately, if the eventual marketed cost of cefonicid is lower than other regimens it may be useful in situations where cost is a factor, such as in public clinics.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Temporomandibular Joint Syndrome

QUESTION:

Is surgical treatment for temporomandibular joint syndrome or maxillofacial pain dysfunction acceptable medical practice?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery, Otolaryngology /Head and Neck Surgery and Plastic Surgery, surgical treatment for temporomandibular joint syndrome or maxillofacial pain dysfunction is acceptable medical practice but is rarely indicated.

If all conservative measures of therapy have failed, surgical operation on the temporomandibular joint may be indicated for carefully selected patients when definite irreversible changes have been shown by clinical examination and supplemented by diagnostic radiography using tomographic x-rays and contrast arthrography; clear evidence of intractable pain and impairment of mandibular mobility is present; all other disease processes which can mimic this syndrome have been ruled out; dental therapy such as dental prosthesis and adjustment of occlusal problems have failed, and the patient is suffering from no psychological disorders.

A number of surgical procedures have been done for the relief of this disorder. These surgical procedures should be done only by those trained and experienced in the management of temporomandibular joint syndrome and maxillofacial pain dysfunction.

A large number of patients suffering from temporomandibular joint syndrome experience pain from muscle spasms caused by psychological disorders. Most of these persons are successfully treated by various conservative methods such as use of a night splint, analgesics, muscle relaxants and supportive psychotherapy.

Original Clinical Articles

Ultrasonic Destruction of Kidney Stones

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Kidney stones may be removed without using a surgical incision by a combination of techniques and skills recently developed in the fields of urology and radiology. Percutaneous access to the kidney is established under fluoroscopic control. A guide wire placed into the renal pelvis allows a nephroscope to be inserted and the collecting system visualized. A long hollow metal probe is advanced through the nephroscope and placed in contact with the stone. This probe conducts the ultrasonic energy. The stone absorbs the energy and breaks into fine granules, which are evacuated by suction.

Twenty-three consecutively seen patients presenting with 27 upper urinary tract calculi for which removal was indicated underwent successful percutaneous ultrasonic lithotripsy. Fifteen stones were located in the renal pelvis, eight in a calix, three at the ureteropelvic junction and one in the upper ureter. One infected staghorn calculus was removed. Two complications resulted in extended hospital stays, but in no patients were surgical incisions required. Of the 23 patients, 9 had previously had a surgical lithotomy. The authors believe that most renal and upper ureteral calculi for which removal is indicated may be extracted percutaneously with the aid of the ultrasonic lithotriptor. The patients may expect a rapid convalescence with diminished pain.

(Brannen GE, Bush WH: Ultrasonic destruction of kidney stones. West J Med 1984 Feb; 140:227-232.)

Removal of kidney stones without using a surgical incision is potentially associated with a shortened and less painful recovery period. Recent technical advances that make possible percutaneous removal of renal calculi include the ability to introduce instruments and drainage catheters into the renal pelvis through a skin puncture, refinements in instrumentation which permit stone manipulation under fluoroscopic monitoring and fragmentation of renal calculi using ultrasonic energy. Percutaneous ultrasonic lithotripsy (PUL) combines these techniques in a joint urologic-radiologic procedure which has been used to remove kidney stones in 23 patients at Virginia Mason Medical Center, Seattle, since November 1982.

Percutaneous access to the kidney and its collecting system, though first reported in 1955,[1] was refined and popularized in the late 1970s.[2,3] Dilation of a nephrostomy tract permits placement of a nephroscope and direct inspection of the renal pelvis and calices. Advances in radiologic instrumentation such as C-arm multidirectional fluoroscopy and steerable catheters permit the percutaneous manipulation and removal of selected renal calculi under combined endoscopic and fluoroscopic control.[4,5]

Fragmentation of renal calculi by ultrasonic energy was pioneered by Alken[6,7] and its application confirmed by Segura.[8] A hollow metal probe to conduct ultrasonic energy is advanced through the nephroscope and placed in direct contact with the kidney stone. Ultrasonic energy (up to 23 MHz) is transmitted to and absorbed by the stone which disrupts into small granules or powder. These fragments are evacuated by irrigation through the nephroscope and suctioned through the probe. This report illustrates the variety of types, sizes and locations of stones that may be removed by PUL.

Patients and Methods

All patients with renal or upper ureteral calculi who would be best managed by operative removal are considered candidates for PUL. The first 23 patients

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ABBREVIATION USED IN TEXT
PUL = percutaneous ultrasonic lithotripsy

treated with this procedure at our institution included 16 men and 7 women. The average age was 51 for men (range 27 to 75) and 47 for women (range 38 to 60). Of the 23 patients, two underwent stone removal by PUL in stages. A difficult caliceal calculus was removed in two stages; a large staghorn calculus was removed in three stages. One patient had a separate PUL procedure carried out on each of her kidneys. In nine patients kidney stones had been removed previously using a surgical flank incision.

PUL Procedure

Under general or regional block anesthesia, a retrograde ureteral catheter (5 or 6 F) is placed via the cystoscope. This allows opacification and distension of the collecting system. The patient is then placed in a prone-oblique position and prepared for a sterile surgical procedure. A 1-cm skin puncture is made below the 12th rib posterolaterally. An 18-gauge needle is inserted through the skin wound and advanced through the renal parenchyma into the calix of choice. If a lower calix contains a stone, it is selected. A more lateral calix is selected for the procedure when the calculus is in the ureteropelvic junction or ureter. A C-arm multidirectional fluoroscopy unit is used to assist the puncture, to verify the needle and catheter positions, and for monitoring of the nephroscope position.

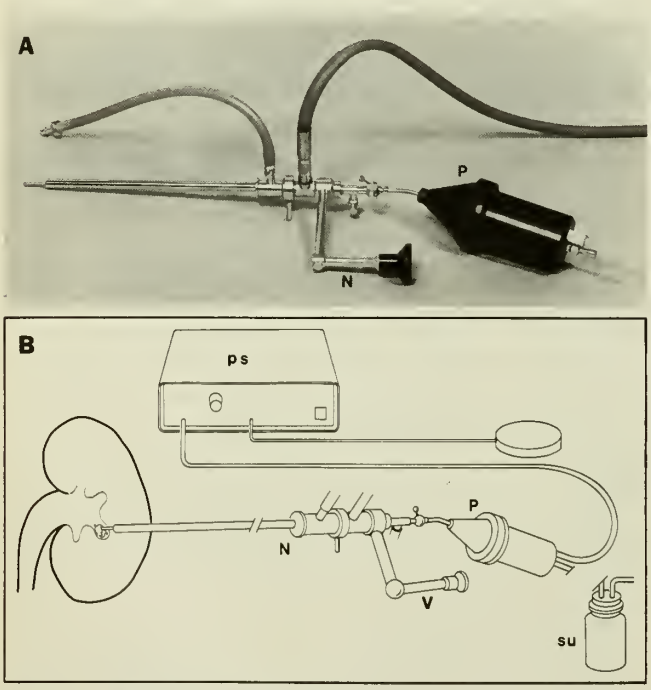

Figure 1.—A, Wolf nephroscope with side viewing arm (N) and ultrasonic probe inserted through the nephroscope (P). **B,** Illustration of Wolf nephroscope (N) with side viewing arm (V) inserted into lower calix of kidney. Ultrasonic probe (P) inserted through nephroscope. Probe connected to power source (ps) and suction (su).

Through the needle a guide wire is advanced into the renal collecting system. Over the guide wire, successively larger polyethylene fascial dilators are placed to enlarge the nephrostomy tract and accommodate the 24 F Wolf nephroscope (Figure 1).

Before the nephroscope is placed, a second guide wire is inserted and a 5 to 6.5 F catheter passed antegrade down the ureter into the bladder. This ureteral catheter provides a backup system for access to the kidney should the nephroscope move out of the kidney during manipulations. In addition, this catheter partially blocks the ureter, preventing stone fragments from entering it. Calculi in the calices or upper ureter must first be moved into the renal pelvis by instrumentation with fluoroscopic monitoring. If the stone is initially in the upper ureter, it is either pushed up into the renal pelvis by retrograde catheter or pulled up into the renal pelvis by a basket or balloon catheter. Fragmentation is done in the renal pelvis.

With the nephroscope in position, the renal pelvis

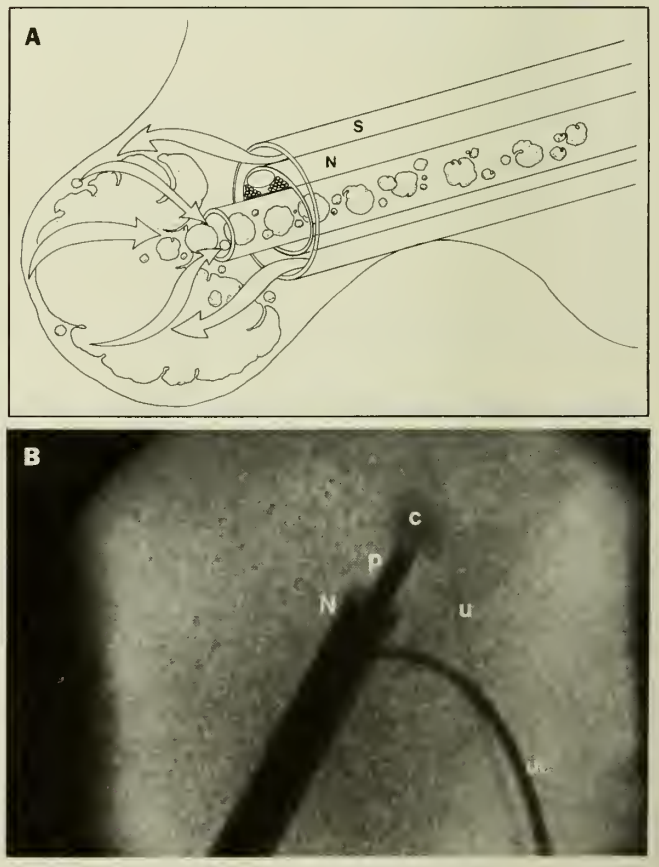

Figure 2.—A, Ultrasonic fragmentation and aspiration of renal calculus. Ultrasonic probe inserted through nephroscope (N), which has been inserted through nephroscopic sheath (S). Following contact of the stone with the ultrasonic probe, fragmentation is initiated. Irrigating solution enters through the sheath and the granules and stone particles are aspirated through the hollow ultrasonic probe. **B,** Fluoroscopic spot film from surgery during ultrasonic fragmentation of renal pelvic calculus (c). Ultrasonic probe (p) has been inserted through nephroscope (N) and is in contact with the calculus (c). Small retrograde ureteral catheter (u) and larger percutaneously placed antegrade ureteral catheter (uc).

and calculus can be viewed directly. The hollow ultrasonic probe is placed through an entry portal in the nephroscope and advanced to contact the stone. Ultrasonic energy is generated to fragment the stone and the resulting granules are evacuated through the hollow probe by simultaneous irrigation and suction (Figure 2).

Once evacuation is complete, the nephroscope is exchanged for an 18 to 22 F catheter which serves as a nephrostomy tube to drain the renal pelvis. The ureteral catheter is left in position and both are secured.

The next day plain film tomograms of the kidney are done to ensure that all stone fragments have been removed. If stone fragments remain, they can usually be removed in the radiology department with the aid of local anesthesia. Instruments introduced through the nephrostomy tract are used to engage the fragment under fluoroscopy and maneuver it out through the tube or tract. This can be done immediately or as a delayed, staged procedure.

With stone removal complete, the ureteral catheter is removed and the nephrostomy tube injected with radiographic contrast material. If the nephrostogram confirms good ureteral drainage, the nephrostomy tube is clamped and removed the next morning before the patient leaves the hospital. Additional days of outpatient nephrostomy drainage may be required in some patients to permit resolution of ureteral edema or slight urinary extravasation. A nephrostomy tube may be left in position for an extended period to provide access for further procedures to remove large or difficult kidney stones.

Reports of Cases

Case 1. A 38-year-old woman presented with intermittent right flank pain. An excretory urogram (Figure 3A,B) defined bilateral renal calculi. On the right, a 10-mm lateral caliceal stone was present and an 8-mm renal pelvic stone obstructed the lower renal pelvis of a duplicated system; in the left kidney, an 11-mm stone was present in the inferior calix.

A right pyelolithotomy had been carried out five years before for removal of a calcium oxalate stone. The cause for the recurrent calculi was believed to be metabolic alterations associated with an intestinal bypass that had been done seven years previously for morbid obesity.

The patient first had a PUL on the right. Cystoscopic passage of a 6 F ureteral catheter moved the impacted lower pelvic calculus into a more accessible position in the renal pelvis. The nephroscope was placed through a lower calix. Then an 18-gauge needle was placed percutaneously parallel to the nephroscope and into contact with the lateral caliceal stone. With fluoroscopic monitoring, the needle pushed the calculus through the infundibulum into the renal pelvis. The two calculi were removed by ultrasonic lithotripsy.

The day after the operation tomography showed three small fragments (2 to 3 mm) remaining in the renal pelvis. A steerable catheter (Meditech, Inc) was passed through the nephrostomy tract and a No. 9 Dormia stone basket passed through the catheter engaged and removed the largest fragment. The smaller two could not be engaged or removed at that time; despite this, the ureteral catheter was removed. The nephrostomy tube was left in position and the patient went home on postoperative day 6 to return for a staged procedure. The second smaller fragment passed spontaneously through the nephrostomy tube. On postoperative day 13, the team extracted the final fragment with local anesthesia through the matured nephrostomy tract

Figure 3.—A, (Case 1) Abdominal film showing two renal calculi on the right (one caliceal and one renal pelvic) and a caliceal calculus in the left kidney. **B,** Urogram shows mild hydronephrosis on the right. The renal pelvic calculus on the right is impacted in the lower renal pelvis of a bifid system (arrow). **C,** Abdominal film shows removal of all right renal calculi fragments before stone removal on the left. **D,** Postoperative nephrostogram following removal of the left caliceal calculus. Contrast material fills the normal system with free flow into the bladder.

using Mazzariella-Caprini stone forceps. The nephrostomy tube was removed on postoperative day 15.

Shortly afterward she had PUL on the left side (Figure 3C,D). The nephroscope entered through the lower calix containing the stone, and it was fragmented and removed from the calix. The left nephrostomy tube was removed on the seventh postoperative day and the patient was discharged on the eighth day free of calculi.

CASE 2. A 32-year-old man had a three-week history of intermittent left ureteral colic. He had passed urinary calculi on three occasions in the past several years. Excretory urography showed two punctate caliceal calculi and a 0.8-cm obstructing calculus impacted in the left upper ureter, about 2 cm below the lower pole of the left kidney (Figure 4A,B). Because of their positions, the two punctate caliceal calculi were not considered for removal.

Percutaneous removal of the impacted ureteral calculus was carried out. Using cystoscopy and retrograde manipulation, the urologist dislodged the stone and pushed it into the renal pelvis. A 6.5 F angiographic catheter was placed in the bladder antegrade through the ureter. A 7 F balloon catheter was also placed in the dilated upper ureter below the stone to maintain the stone position at the ureteropelvic junction during fragmentation and to retain stone fragments in the renal pelvis during PUL.

Tomography and a nephrostogram showed all fragments were removed (Figure 4C,D). The patient was discharged on the fifth postoperative day; the nephrostomy tube was removed 3 days later, and he returned to fulltime work 10 days after the procedure.

CASE 3. A 27-year-old man, a respiratory therapist, had an infected staghorn calculus in his solitary left kidney, found during evaluation for persistent urinary tract infection (Figure 5A,B). Urine culture continued to grow *Pseudomonas* sp despite antibiotic administration. The branched calculus measured 6 by 9 cm. The serum creatinine concentration was 1.4 mg per dl.

Congenital bladder outlet obstruction had damaged both kidneys. At age 6, right nephrectomy and urinary diversion of his left kidney had been done. A left pyelolithotomy had been carried out at age 17. Existing urinary drainage was by means of a colon conduit which transported urine from the left renal pelvis to a skin stoma.

The large staghorn calculus was entirely removed by ultrasonic lithotripsy in three sessions at intervals of two weeks. For all procedures, the calculus was approached through the colon conduit. After the first session of one hour, 30% of the calculus had been removed (Figure 5C). After the second session of two hours, only three large fragments remained (Figure 5D). The third two-hour session completed removal of these fragments (Figure 5E). Total hospital confinement of this patient was four days.

The patient subsequently had anastomosis of the enteric conduit from the left renal collecting system to the bladder.

Results

In this series of 23 patients, 27 stones were removed. Fifteen were located in the renal pelvis, eight in a calix, three impacted within the ureteropelvic junction and one in the upper ureter.

Patients' time under anesthesia for the procedure varied from two to five hours (average three hours six minutes). Fluoroscopy time varied from 13 to 65 minutes (average 29.2 minutes). In three patients transfusions were required to replace blood lost during the perioperative period. Hospital stays averaged 4.6

Figure 4.—A, (Case 2) Abdominal film of patient with upper left ureteral calculus (arrow). **B,** Urogram showing partial obstruction of the upper left ureter and collecting system by the calculus (arrow). **C,** Tomogram following ultrasonic removal of left calculus reveals no residual fragment. The stone had been moved up into the renal pelvis prior to ultrasonic fragmentation. **D,** Nephrostogram on postoperative day 2 following removal of ureteral catheter. Moderate edema about the ureteropelvic region of the collecting system; additional days of outpatient nephrostomy drainage were required to permit resolution of ureteral edema.

postoperative days (range 2 to 15 days). The nephrostomy tube was removed after 6.2 days on the average (range 2 to 16 days).

Twenty-seven stones in 23 patients were targeted for removal by PUL. Seventeen patients had complete removal of the targeted calculi at the primary PUL procedure. Three additional patients had complete removal of targeted calculi by PUL with the aid of an adjuvant procedure under local anesthesia in the radiology department. In one patient with a difficult caliceal calculus, two stages were required for removal. A large staghorn calculus was removed in three PUL sessions. A single patient with incomplete removal of a renal pelvic calculus will be discussed in the Complications section below. Since beginning to use the PUL procedure in our institution, no patient has had a surgical incision for primary stone therapy or for management of untoward events associated with PUL.

Complications

Two of these initial 23 patients suffered complications requiring prolonged hospital treatment or readmission. In a third patient with delayed urinary bleeding, neither blood transfusion nor hospital admission was required.

One patient suffered rupture of the renal pelvis with retroperitoneal extravasation of stone fragments and sterile irrigating water. The procedure was continued in an effort to retrieve the retroperitoneal fragments. Absorption of the irrigating fluid resulted in water intoxication and hemolysis. Although the patient was obtunded during the night after operation, she was alert the following morning. Several days later, the sudden onset of renal bleeding required blood transfusions but resolved spontaneously. The nephrostomy tube was removed on the tenth postoperative day. She was discharged 15 days following PUL. The staff feels

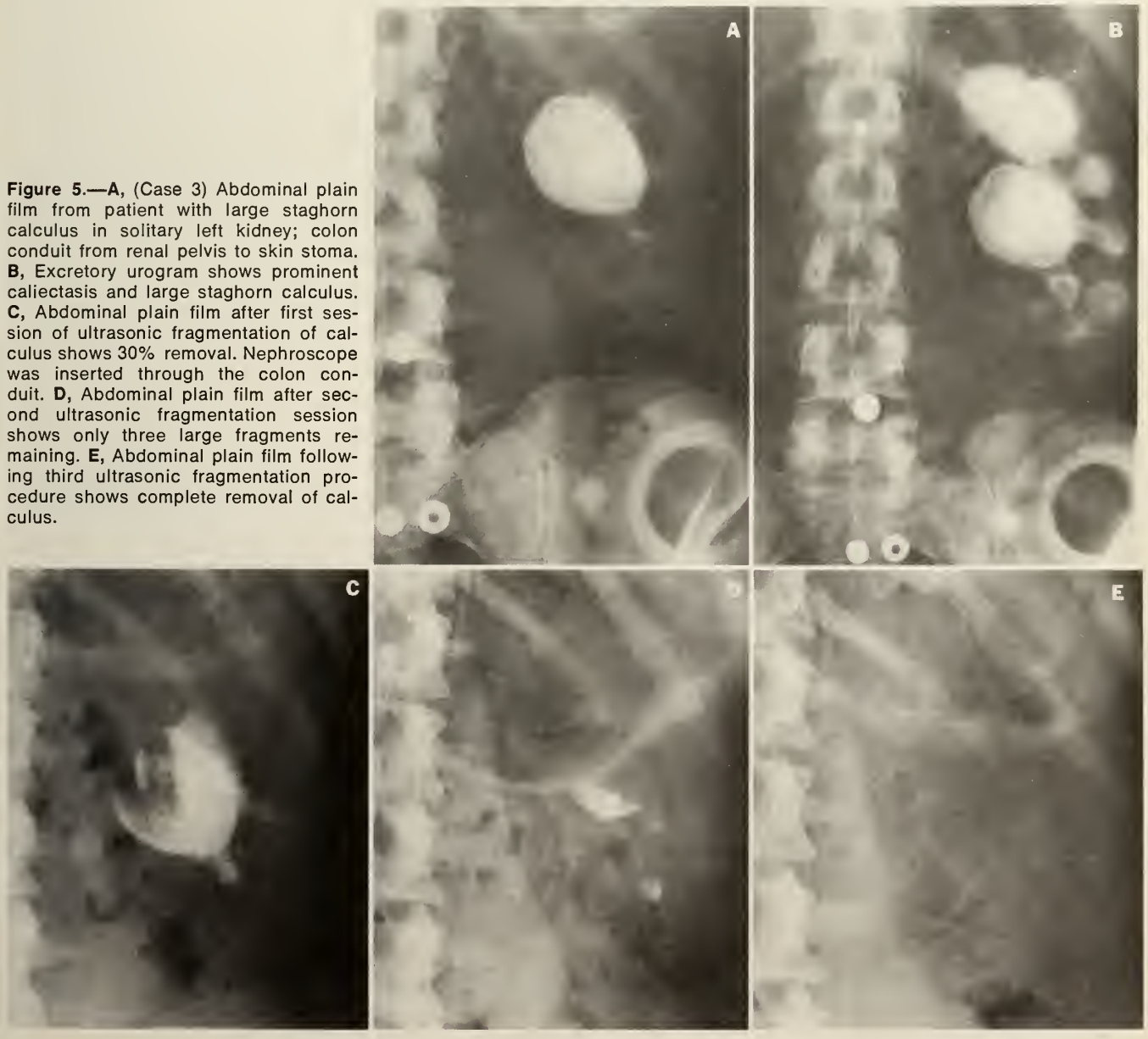

Figure 5.—A, (Case 3) Abdominal plain film from patient with large staghorn calculus in solitary left kidney; colon conduit from renal pelvis to skin stoma. **B,** Excretory urogram shows prominent caliectasis and large staghorn calculus. **C,** Abdominal plain film after first session of ultrasonic fragmentation of calculus shows 30% removal. Nephroscope was inserted through the colon conduit. **D,** Abdominal plain film after second ultrasonic fragmentation session shows only three large fragments remaining. **E,** Abdominal plain film following third ultrasonic fragmentation procedure shows complete removal of calculus.

that the stone fragments may safely remain outside of the renal pelvis in the retroperitoneum.

The authors believe that PUL procedures are best initiated using sterile water as an irrigant for optimal visualization of the renal collecting system. In the event of a disruption of the renal pelvis, the irrigating fluid may be changed to normal saline and the procedure shortly terminated. When a major rupture of the renal pelvis is identified, the procedure should be promptly terminated, leaving the renal pelvis to nephrostomy drainage. After the renal pelvis has healed, retained fragments may then be removed through the same nephrostomy tract.

A second patient had symptomatic (pain and fever) urinary extravasation following early postoperative dislodgement of a nephrostomy tube. The difficulty was resolved shortly after the nephrostomy tube was repositioned in the radiology department. The nephrostomy tube was left to drain until he was readmitted two weeks later for PUL with removal of a difficult caliceal calculus. One day after discharge from the hospital he returned with flank pain, fever and gross hematuria. The problem was rapidly resolved with the aid of bed rest and parenteral antibiotics; blood transfusion was not required. He was discharged from the hospital symptom-free.

In one patient passage of bloody urine and clots occurred three days after removal of his nephrostomy tube and discharge from the hospital. A Foley catheter was placed to relieve an episode of urinary retention from blood clots. Neither hospital admission nor blood transfusion was required. The appearance of hematuria coincided with the conclusion of a prolonged automobile trip (several hundred miles). The staff now advises limited physical activity and limited travel during the first two weeks after PUL.

Discussion

The most obvious advantage of PUL over conventional surgical lithotomy is the potential for the patient to experience a shorter and less painful convalescence. Wound-associated problems such as cutaneous numbness, muscle weakness, abdominal bulging, incisional herniae and wound infections are virtually eliminated by the use of percutaneous surgical operation. Stone fragments retained following PUL may be retrieved through the existing nephrostomy tract using local anesthesia. Small caliceal stones may be difficult to locate and retrieve during surgical exposure of the kidney. Such stones may be more easily accessible during PUL with the aid of sophisticated radiologic instrumentation under fluoroscopic control.

Operative risks include immediate or delayed bleeding, renal or perirenal infection, ureteral stricture formation and urinary extravasation. These risks are similar to those associated with surgical lithotomy. Associated with PUL but not with surgical lithotomy is the risk of water intoxication secondary to intraoperative absorption of irrigating fluid. The staff believes this complication can be avoided and that other risks will diminish with increased experience of the staff. Castaneda-Zuniga and co-workers[4] reported a 3% complication rate using percutaneous techniques to remove 63 stones in 25 patients. Although 2 of our initial 23 patients had complications leading to additional hospital treatment and morbidity, no patients have had complications requiring surgical intervention.

Conventional surgical lithotomy involves a 20-cm long incision and division of three muscle layers, resulting in considerable postoperative pain and a long convalescence. Average hospital stay is one to three weeks with an additional four to eight weeks of recuperation at home.[4] PUL requires an average hospital stay of 4½ days with rapid return to normal activities.[8]

Our experience shows the potential usefulness of PUL for all renal or upper ureteral calculi for which removal may be indicated. Such calculi include those located in the renal pelvis, calices and upper ureter, as well as staghorn and infection stones. Calculi which are generally not approachable by PUL or by surgical lithotomy include punctate caliceal calculi, renal parenchymal stones and diffuse nephrocalcinosis. Since the risks of PUL seem equable with those of surgical lithotomy, the authors feel that PUL may be exchanged for surgical lithotomy as the primary procedure for removal of kidney stones. Pain and time in hospital are decreased and patients may expect a rapid convalescence.

Addendum

Since the submission of this manuscript an additional 138 patients have been treated, bringing our experience to 161 cases. A single patient required surgical removal of a kidney stone following unsuccessful efforts at percutaneous ultrasonic lithotripsy. No complications have required surgical management.

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Compensation and Recovery From Injury

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Workers' compensation laws influence recovery from injury. They affect the "cause" of disease, access to care, diagnostic evaluation, treatment, response to treatment and residual disability. Paradoxically, financial compensation may discourage return to work, the appeal process may increase disability, an open claim may inhibit return to work and recovering patients may be unable to return to work.

Physicians may help improve the prospects of returning patients to work by providing care that is medical, caring and independent. It is essential that the treatment of back pain be based on the known natural history and on the understanding that the management of acute pain differs from that of chronic pain.

Increased awareness of the factors controlling return to work should motivate legislative bodies, labor and industry to alter those features of the compensation system that interfere with the return to work of injured workers.

(Beals RK: Compensation and recovery from injury. West J Med 1984 Feb; 140:233-237.)

In 1911 workers' compensation laws were enacted in the United States requiring employers to assume the cost of occupational disability without regard to fault. The resulting financial losses were to be considered costs of production.

There are five basic tenets of the workers' compensation laws:

- Cover work-related injuries
- Protect income
- Provide medical and rehabilitative services
- Encourage safety
- Encourage effective delivery of benefits.

The benefits include cash payment, medical care and rehabilitative services. The cash benefits may be for temporary or permanent disability and for partial or total disability.[1]

The objectives seem reasonable; yet, this system has been described by Kessler as "the etiologic factor responsible for the prolongation of symptoms and the production of the neurotic behavior on which prolonged disability is based."[2]

The terms "compensation neurosis" and "traumatic neurosis" are not new. They were coined by European physicians of the late 1800s who observed that their accident laws were "the soil upon which the traumatic neuroses have grown" and that "many malingerers had been cured by successful suits at law." While the "disability process" may be a more common term today, there is little to argue with Crenshaw's observation in regard to compensation that "human nature changes little with the times."[3]

More than 70 years of experience with workers' compensation laws have produced limited information about the mechanisms by which the compensation system influences disability. I will describe some of the effects of the compensation system on recovery from injury and offer some suggestions for remedy. The main focus of this presentation will be back injuries.

Effects of the Workers' Compensation Laws on Recovery From Injury

Our compensation laws and system influence the "cause"' of disease, access to care, patterns of disease, diagnostic evaluation, treatment, response to treatment and residual disability.

The 'Cause' of Disease

Studies of the frequency of injury as a cause of sciatica show widely discrepant findings. Injury has been reported in 92% of patients with sciatica in the United States, 59% in Great Britain and 22% in Sweden.[4-6] The obvious explanation for this discrepancy lies in our compensation laws, which require an injury

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before compensation. When injuries are not required for coverage, they "occur" less often.

These findings highlight the fact that coverage by industrial accident insurance relates to the manner in which *both* patient and doctor represent the problem to compensation boards. It is often difficult to determine if an injury truly arose out of a person's employment. The degree to which preexisting factors are recognized and the nature of an acceptable injury receive varied interpretations. If a patient or a doctor begins a professional relationship with hostility or in a compromised ethical state of mind, the results of treatment may also be compromised.

Access to Care

The incidence of injury is a determinant in establishing insurance rates. In an effort to improve work-safety records, some injuries are not reported and injured patients are not treated promptly. Rather, injured workers are encouraged to go to work—sign in—and do nothing, in hopes of a spontaneous improvement. The wrong "practitioners" may decide whether or when treatment is indicated. When industrially injured patients do seek or are sent for medical care, patterns of referral exist that limit a patient's freedom of choice and tend to stereotype treatment, whether or not it is effective.

Pattern of Disability

The accident-compensation plan in New Zealand at one time included the provision that the wages of a worker injured on the job were to be continued at *full rate* for the first week. Thereafter the rate would drop. Shortly after its inception there was a pronounced increase in absenteeism due to injury (" 'Strains and Sprains' in Freezing Works Costly," *New Zealand Herald,* November 8, 1976). Officials acknowledged that "Many men with minor injuries who in the past would get some first aid and return to work are currently going on compensation the first week" ("Helping the Hurt: To Accident Victims, New Zealand Offers the Balm of Money," *The Wall Street Journal,* September 16, 1975, Vol 93, p 54, col 1). In this environment the pattern of disability is set "by law" and it would be naive to expect a prompt return to work.

Diagnostic Evaluation

The number of diagnostic tests and x-ray studies ordered have been shown to be related to the availability of insurance coverage.[7] This not only increases expense, but may not be to patients' benefit. Unnecessary admissions to hospital and huge packets of x-ray films reinforce patients' belief that their problem is serious. In some practices it is customary to do a myelogram in an effort to "prove" that a herniated disc is *not* present. The finding of abnormal discs by myelography in 25% of asymptomatic patients underscores only one of the hazards of this approach.[8]

Treatment

Patients receiving compensation tend to receive *more* treatment than those who do not. Krusen and Ford studied patients admitted to hospital with back injuries. They found that those receiving compensation showed 33% less impairment than noncompensated patients, yet they received 200% as many physical therapy treatments.[9] Inpatient data such as these likely represent merely the "tip of the iceberg," as one of the most characteristic features of outpatient medical care of industrial workers has been the reluctance to discontinue ineffective therapy.

Response to Treatment

Patients receiving compensation for a back injury respond less well to treatment than those who are not being compensated. Krusen and Ford reported 44% less long-term improvement in compensated patients with back complaints; Mensor reported 19% fewer satisfactory results with manipulation for low back pain; Slepian had 30% fewer satisfactory results from disc surgical repair, and Flynn and Hogue reported 40% fewer good results in patients who had anterior spine fusion.[4,9-11]

Residual Disability

Residual disability is greater in compensated than in noncompensated patients. Disability is in large measure behavioral. Behavior is learned. Disability determines the amount of compensation. Therefore, compensation is based in part on learned behavior. Behavior reflects motivation and a patient's perceived success in returning to work. Behavior also reflects how a patient might fare if he or she does *not* return to work. Thus, there are patients with minimal impairment who are greatly disabled and patients with great impairment who are minimally disabled.

Compensation Systems of the Pirates

Compensation systems are not new in organized society. To provide some perspective of our system, it might be of interest to examine features of another compensation system, that of the pirates of the 18th century. Piracy has been described as the third oldest profession, ranking only behind prostitution and medicine. Piracy occurs today and has always existed wherever the rewards of the crime have justified the risk of punishment. It was the British who developed piracy into its most refined form, being encouraged and rewarded by the British monarchs.

The "golden age of piracy" developed in a harsh social and economic system that led those buccaneers to be "passionate advocates of a rude sort of democracy, with a high regard for justice and the rights of the individual, and a corresponding distaste for tyranny and the abuse of power."[12]

Pirates had a fairly standard system of operation. First, they acquired a ship. Their sailing Articles provided for payment of operating expenses and for the division of profits. Operating expenses included costs of the ship, provisions, a surgeon, a shipwright, sometimes a sailmaker and compensation for disability. After subtracting operating expenses they divided the

profits, their elected captain receiving the greatest amount.

Surgeons were normally hired on contract and did not share in the spoils. They spent most of their time treating venereal disease and helplessly observing the ravages of yellow fever, malaria and dysentery. In combat they dressed wounds and amputated limbs. In the event that a ship had no surgeon these duties fell to the shipwright (or carpenter) as "the tools were much the same."[12]

The entire venture was based on the premise that pay was not guaranteed. Their disability costs included both scheduled and unscheduled benefits. An example of scheduled compensation is as follows:

For Loss of	*Pieces of Eight Awarded*
Right arm	600
Left arm	500
Right leg	500
Left leg	400
An eye	100
Finger	100

Unscheduled disability was evaluated by a surgeon and the disability quantitated in one of two classifications: hurt or crippled. For example, "Our surgeon [evaluated] the wounded [finding] four crippled and six hurt, to whom we gave 600 pieces of eight a man and a thousand to those who were crippled, as was our custom."[13]

Other features of their system included a lack of death or retirement benefits, no appeal and the feature of lump sum payment. Vocational rehabilitation was available for some—that is, "Many a peg leg clomped over the pirates' decks earning a half share of plunder as a cook, no matter how little he knew of the culinary arts."[12] Even social security in a crude form (for job-related injuries) existed as exemplified by the documentation that "Shipmates who had lost eyes or limbs in piratical combat were allowed to live on board as long as they chose."[12]

Piracy should not be romanticized—yet, these practices illustrate the fundamental need and desire for medical care and rehabilitative services for those injured on the job. We can concur in the desirability of such care but we must observe that the system we use often interferes with or prevents recovery and return to work.

Loren Eiseley, the great naturalist, scientist and humanist, wrote an essay on the root cause of declining civilizations. He traces the development of human society, noting that with increasing size of a population there is decreased citizen input to government and the development of inefficiency, graft and rigidity within a bureaucracy that resists change. He states, "There tend to rise in human civilizations institutions which monopolize . . . the wealth and attention of society . . . to its detriment."[14] He refers to these institutions as "cultural overgrowths, excessively ornate societal excrescences as exaggerated as some of the armour plate that adorned the gigantic bodies of the last dinosaurs."[14]

The compensation system is surely what Eiseley would call a cultural overgrowth. Excessively elaborate and irrational compensation rules are proving to be detrimental to both injured humans and society.

The Paradox of Compensation Laws

A paradox is an observation that seems to contradict common sense. It is not contrary to reason; it just at first appears to be. Paradoxical features of the compensation system interfere with recovery and must be altered by legislative, executive or judicial bodies or by industry or labor unions if patients are to be given a maximal opportunity to return to work. Four examples of these paradoxes are provided.

Paradox I

Financial compensation discourages return to work. An important variable affecting return to work not normally evaluated by doctors is the amount of financial hardship incurred by unemployment. Some injured workers do not share a tradition of professionalism or pride of workmanship that characterizes the majority. They work primarily for income. Patients often assert that being unable to work is a great financial hardship, yet this is often not so. In Oregon the stipend for temporary total disability is two-thirds of the *gross* wage up to 100% of the average wage. The stipend for permanent total disability is two-thirds of gross wage to a maximum of $14,917 per year—not until age 65, but until death—plus a dependent allowance.[15] This tax-free income may not constitute a significant financial hardship. Other factors that must be taken into consideration are the number of wage earners or other sources of income in the family, and whether the injured persons have private disability income or insurance.

There is a need to limit total financial compensation for *not* working. When the real income associated with continued disability approaches or exceeds that when working, any form of treatment is likely doomed to failure.

Paradox II

The appeal process increases disability. One might think that an appeal process is designed to right a previous wrong, but evidence suggests that that is often not what occurs. Patients with residual pain and impairment may feel that the proffered award is less than appropriate. If an award is appealed, legal counsel is usually involved.

In a study of patients in Oregon who had had back operations who appealed their disability awards it was found that the average final disability award in the appealing group was twice that of those who did not appeal. Yet, there were no organic differences between the two groups of patients (R. A. Martin, MD, "A Study of Back Surgery," Department of Public Health and Preventive Medicine, The Oregon Health Sciences

Center, and Medical Director, Oregon Workmen's compensation Board, April 1975, written communication). The obvious implication is that the appeal process increased disability without changing impairment. In 1977 and 1978 the hearings division of the Workmen's Compensation Board of the State of Oregon increased the awards in 80% and 73% of cases they reviewed.[15]

The association of the greatest financial reward for lawyers and workers by establishing the greatest amount of societal labeled disability is a regrettable feature of the compensation system. There is a need to develop evaluation systems that base compensation on impairment.

Paradox III

An open claim inhibits return to work. Claims are closed by law when a steady state of disability has been reached. Patients who are symptomatic are loathe to have their treatment stopped or their claims closed. For a claim to be open, the patient must be getting better, getting worse or be under a treatment program. Many treatment programs can be described as "Brownian movement," producing little or no real change.

The effect of an open claim is shown by Gotten's study on cervical strain. A follow-up study of 100 patients following claim closure disclosed that whereas 41% of the patients were off work for three months before settlement, only 7% remained disabled after claim closure. He noted, "One cannot help but deduce that settlement of claims definitely influenced the symtoms advantageously."[16]

There is a need to develop mechanisms to stop ineffective therapy and close claims in order to maximize recovery and return to work. Patients should not be rewarded for continued disability but rather for return to work.

Paradox IV

Recovering patients are often unable to return to work. To return to maximal performance, injured athletes must keep regular hours, control weight, avoid drugs, develop strength and practice motor skills. Persons who do physical work for a living should do the same. Yet, patients recovering from injuries are often found to be overweight, taking drugs, undisciplined and unfit. Even when they become capable of light work, the rules of many unions and employers preclude return to work unless they are totally fit and able to do heavy work.

The psychological and physiological needs of patients must be recognized to allow recovering workers to return to a work environment where they can develop good work habits, build strength and acquire agility with the goal of returning to their previous job or, if unable, to a less physically demanding job.

Prescription for Medical Management of Industrially Injured Workers

It is not difficult to point out deficiencies in the compensation system that interfere with successful patient management. More sobering, but necessary, is that we also critique our medical management of such patients. I should like to offer three suggestions for improving our medical management.

1. *Physicians should direct the medical care of patients.* The essential role of physicians is to provide care in a setting that is *medical, caring and independent.* When we stray from this role, problems tend to develop.

Medical care should be medical. Physicians are not trained, nor should they be expected, to be a patient's advocate. Inappropriate advocacy by treating physicians may be subtle and take several forms, such as continuing ineffeective therapy, recommending vocational rehabilitation following minor injury, becoming a patient's "representative" to a Workers' Compensation Board, or advising a patient how to deal with legal counsel or insuring agencies.

Medical care should be caring. Medical consultation requested by a treating physician is always welcomed but the need for and value of independent medical evaluations should be reexamined by those requesting them and by those providing them. Independent medical evaluations are too frequently neither "independent" nor "medical." These evaluations may not be classically "medical" because the examiners do not anticipate providing assistance to a treating physician. Examiners often speak to the psychological state or the motives of a patient, although not qualified to do so. "Independent" examiners are often chosen because their responses are predictable and authoritative. If multiple examiners are involved, there is more authority, but rarely more medical sophistication. This type of examination destroys a patient's confidence in the medical care system and reinforces the patient's perceived disability.

Medical care should be independent. The Workers' Compensation Board in Oregon chose to build a multimillion dollar treatment center and staff it with physicians employed by the Board. It is no secret that the center has enjoyed limited success. To succeed, it would have to be staffed by fiercely independent physicians, as it is vital to patients that medical decisions be, and be perceived to be, independent of the compensation board.

2. *The management of back pain should be based on the known natural history.* Patients with acute back pain and no previous surgical procedure can anticipate a 60% chance of recovery in three weeks and a 90% chance of recovery in eight weeks.[17] Patients whose back pain persists after two months can expect some increased chance of recovery for one year.[18] White found that nonoperative care of industrially injured workers resulted in an increase in satisfactory results for up to three years of treatment.[19]

When this reported natural history with conservative care is contrasted with the results of our treatment, it gives pause for reflection. Martin reported a follow-up study of all acute industrial back sprains that occurred during one month in Oregon. At the end of

one year, 15% had been given partial disability and 6% had been treated operatively (R. A. Martin, MD, "A Study of Time Loss Back Claims," Workmen's Compensation Board, State of Oregon, written communication, March 1971). This suggests that we should take a hard look at our therapy.

3. *The management of patients with chronic back pain should be different from the care of acute back pain.* Almost everything we do for acute back pain is the wrong treatment for chronic back pain. In acute low back pain the evaluation may be simple and patient involvement in recovery is minimal. The focus is on pain that can normally be treated with drugs and rest. In chronic low back pain the evaluation must be comprehensive and patient participation is mandatory for recovery. The focus is on behavior, and recovery is interfered with by drugs and lack of activity.

Successful management of patients who have chronic pain and disability often requires an evaluation of psychosocial factors that both preexist and develop following injury. Preexisting factors that "cause" injury are not precisely defined, yet they exist. A strong case has been made to support the concept of the "accident process" in which the accident itself and the subsequent symptoms represent a solution to life's problems.[20] Life stresses as measured by high scores on the Life Change Unit Value scale have been found by Meyers to *precede* injury in Southern Pacific workers (J. E. Meyers, MD, "Overview by Industry of Lumbar Spine Pain Problems," written communication, 1979). Other studies have indicated that patients with back disability have a higher incidence of previous alcohol and drug abuse and are more likely to have been off work for medical reasons aside from back pain.[21]

Postinjury factors include abnormal psychological responses to injury. People regard their backs as symbols of health and the ability to cope in a complex world. This symbolism is beautifully described by Melville in *Moby-Dick* when he has Captain Ahab say,

> For I believe that much of a man's character will be found betokened in his backbone. I would rather feel your spine than your skull, whoever you are. A thin joist of a spine never yet upheld a full and noble soul. I rejoice in my spine, as in the firm audacious staff of that flag which I fling half out to the world.[22(pp346-347)]

Management of patients with chronic back pain is difficult at best, but nearly impossible by solo physicians.[23] The most effective results occur using a multidisciplinary approach and behavioral training. In one study the patients were treated by admission to hospital and team management including guided physical therapy, supervised medication production, relaxation therapy, behavioral training and participation of the family in the therapy program. In this group of 60 patients, half showed an increase in activity in a work-like situation and 20% returned to work.[24] Yet, another study found that 88% of industrially injured workers could return to full activity after treatment in a hospital rehabilitation program, though 20% could not find employment because of their medical history.[25]

In patients with chronic back pain, treatment must be directed to the "whole person," taking into account all the variables that influence a successful return to work. Undue focus on the organic aspects of chronic back pain will often lead to failure of recovery. As Claude Bernard wrote, "The greatest error in the advancement of medical science has been the search for a single cause for a single disease."[26]

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Advances in Diagnosis and Management of Salivary Gland Diseases

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Salivary glands may be involved in a wide variety of diseases, which may be broadly grouped into (1) inflammatory, (2) noninflammatory, nonneoplastic and (3) neoplastic categories.

Most inflammatory and noninflammatory, nonneoplastic diseases should be managed conservatively and symptomatically. The common exceptions are first-arch branchial-cleft cysts and calculi.

Neoplastic lesions always require resection if that is feasible. For benign tumors, simple excision with a cuff of normal tissue around it will usually suffice. The prevailing trend for treatment of malignant neoplasms is conservatism. No longer is the facial nerve routinely sacrificed. The resection done is dictated by the tumor size and the facial nerve is spared unless directly invaded. Postoperative radiation therapy is increasingly used.

(Rice DH: Advances in diagnosis and management of salivary gland diseases [Medical Progress]. West J Med 1984 Feb; 140:238-249.)

This review is intended to be an update on current concepts of the diagnosis and management of nonneoplastic diseases of the salivary glands. In addition, there is an extremely brief review of general principles in the management of neoplastic lesions.

The embryology, microscopic and gross anatomy, physiology and biochemistry are briefly reviewed. The importance of saliva in the health of the teeth and mucosa is discussed as well as its antibacterial, antiviral activity.

Embryology

The embryology of the salivary glands is incompletely understood. The major salivary glands and the minor glands anterior to the anterior tonsillar pillars are believed to be derived from ectoderm, whereas the remaining glands are derived from endoderm. Regardless, there is no histologic difference between the two areas and no difference in the tumors that occur there.

Histology

The mature salivary gland unit begins as a serous, mucous or mixed acinus. Each acinus empties into an intercalated duct, which leads to a striated duct that empties into an excretory duct. Each segment has specialized functional and morphologic characteristics.

Acinar cells are highly differentiated cells responsible for the production of mucinous or serous secretions. Parotid acini are predominantly or exclusively serous, whereas submandibular acini are of a single type called seromucous.[1] The mucous acini of the sublingual gland resemble those of the submandibular gland.

The cuboidal cells of an intercalated duct are relatively unspecialized. The striated duct cells are well differentiated and have features that are similar to renal proximal tubule cells. The striated duct cells play an important role in electrolyte and water transportation. The basal cells of the intercalated and excretory ducts act as reserve cells for the most differentiated cells of the salivary gland unit. These reserve cells are responsible not only for normal salivary gland development but also for tumor formation.[2] It is now generally agreed that salivary gland tumors arise from one of these two cells, and data from both light and electron-microscopic studies support this theory.[3]

Gross Anatomy

The parotid gland is the largest salivary gland and lies anterior and inferior to the ear. It overlies the

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upper quarter of the sternocleidomastoid muscle and the masseter muscle.

The submandibular gland occupies most of the submandibular triangle. The inferior surface lies adjacent to the anterior and posterior bellies of the digastric muscle. Anteriorly the gland lies directly on the mylohyoid muscle. The sublingual gland lies below the mucosa of the floor of the mouth anteriorly, superficial to the mylohyoid muscle.

Physiology

The secretory unit of a salivary gland is composed of an acinus, an intercalated duct and a striated duct. Acinar cells are arranged around a central lumen and have contractile myoepithelial cells interposed between them and the basement membrane peripherally. Serous cells produce a watery secretion containing neural carbohydrates; mucous cells secrete a viscous solution with mucopolysaccharides; seromucous cells secrete both. Protein is synthesized by the ribosomes on the endoplasmic reticulum and is transported first to the cisternae of the endoplasmic reticulum and then to the Golgi apparatus. The latter is the site of carbohydrate synthesis and plays a key role in the elaboration of mucus. In serous cells, the secretory granules discharge their contents by establishing a continuity between membranes of a granule and the apical cell surface. For mucous cells, secretory granules are discharged through gaps in the cell surface.

Secretion is controlled by physical and psychic stimulation mediated through the autonomic nervous system. Physical stimuli from the oral cavity and psychic stimuli from taste, smell or sight centers travel afferent pathways to the superior and inferior salivatory nuclei. Both sympathetic and parasympathetic pathways are involved. The control of secretion is complex (Table 1). Parasympathetic and sympathetic innervation affects acinar cells differently, and the α- and β-adrenergic innervation may also have different effects. The autonomic innervation also affects the duct cells, which are involved in the active transport of electrolytes.

Biochemistry

Numerous factors influence the composition of saliva. The collection technique itself will produce either whole saliva or the secretions of a single gland, and either stimulated or unstimulated saliva. The use of whole saliva in which a person expectorates into a container is not ideal, because it is impossible to accurately determine the flow rate that alters the concentration of many constituents and because it is contaminated by desquamated cells, food particles, bacteria and other debris.

The salivary flow rate is variable. There is a diurnal variation with reduced production in the early morning and increased production in the afternoon.[4] The rate is near zero during sleep, but may reach 4 ml a minute during maximal stimulation. The average volume per day has not been well studied and is difficult to measure accurately. The measured volume per day in two patients with esophageal-cutaneous fistulas averaged 500 ml.[5] These patients, of course, were not eating.

The specific gravity of saliva varies from 1.000 to 1.010, increasing with faster flow. The relative viscosities after stimulation are as follows: parotid, 1.5, submandibular, 3.4, and sublingual, 13.4 centipoises.[6] The viscosity is directly related to the percentage of mucous cells. The pH is slightly acidic before secretion into the oral cavity, but becomes slightly alkaline on entering the oral cavity due to the loss of carbon dioxide. Because the bicarbonate concentration increases with rising flow rate, the pH becomes elevated at high flow rates. About 90% of the total volume of saliva comes from the parotid and submandibular glands in about equal amounts.

The mean concentrations of some of the substances found in saliva are shown in Table 2. The flow rate can significantly alter some of these values in that as it increases, sodium and bicarbonate levels and pH rise, while potassium, calcium, phosphate, chloride, urea and protein levels fall.

Other factors influence the composition of saliva independently of the flow rate (Table 1). A high-

TABLE 1.—*Factors Affecting Flow Rate and Composition of Saliva*

Drugs
Cocaine, strychnine, reserpine, morphine, digitalis, quinidine, muscle relaxants, anti-parkinsonism drugs, theophylline, sympathetic and parasympathetic drugs
Loss of Functioning Gland Substance
Irradiation, aplasia, chronic inflammation, ductal obstruction
Hormonal Changes
Cushing's disease, Addison's disease, aldosteronism, menstruation, pregnancy
Mucous Membrane Irritation
Smoking, quinine, peppermint
Disrupted Fluid and Electrolyte Balance
Diabetes insipidus, diuretics, dehydration, uremia

TABLE 2.—*Composition of Saliva*

	Salivary Gland	
Substance	*Parotid mEq/liter*	*Submandibular mEq/liter*
Potassium	20.0	17.0
Sodium	23.0	21.0
Chloride	23.0	20.0
Bicarbonate	20.0	18.0
Calcium	2.0	3.6
Magnesium	0.2	0.3
Phosphate	6.0	4.5
	mg/dl	*mg/dl*
Urea	15.0	7.0
Proteins	250.0	150.0
Ammonia	0.3	0.2
Uric acid	3.0	2.0
Lysozymes	2.3	1.5
Glucose	<1.0	<1.0
IgA	4.0	2.0
Amylase	0.1	0.0025
Cholesterol	<1.0	unknown
pH	5.92	5.73

protein diet increases the urea concentration. The sodium concentration is altered by aldosterone, glucocorticoids and adrenocorticotropic hormone. The concentrations of iodide, calcium and bicarbonate depend on the plasma concentration. The concentrations of urea and uric acid are related to the blood levels, and the effectiveness of hemodialysis can be followed by parotid salivary analysis.[7]

Amylase is the main protein in parotid saliva. The major protein constituents of the more mucus-secreting glands are the glycoproteins, especially sialic acid. About 75% of people secrete a glycoprotein named blood group substance in their submandibular and sublingual saliva. Blood group substance is responsible for blood type, and thus blood type can be determined in secretors by salivary analysis. Another glycoprotein produced by the parotid and submandibular glands is secretory piece, which binds two molecules of immunoglobulin A to stabilize this IgA and form secretory IgA.

Function of Saliva

The composition of saliva endows it with several important physical and biochemical properties. The mucous layer protects the oral mucosa from local irritants and from desiccation. Further, the mucus takes a relatively direct and constant course in the oropharynx, sweeping microorganisms and foreign particles with it for destruction and elimination by the gastrointestinal tract.[8] The glycoproteins in saliva lubricate the tongue, oral mucosa and teeth to facilitate speaking and swallowing.

Saliva protects the teeth. The lubricating function reduces wear. The minerals aid in posteruption maturation and calcium and phosphate help prevent enamel dissolution in plaque. Bicarbonate and phosphate exert antibacterial activity within plaque by their buffering capacities.

The importance of saliva in protecting teeth is well illustrated by the pronounced increase in caries seen following radiation therapy to the oral cavity. Irradiation causes a great reduction in salivary flow rate—95% and more after full-course radiation therapy—and this reduction persists indefinitely.[9,10] Morphologic studies have shown that serous acini are destroyed, whereas there is little discernible change in the mucous acini.[11] Because of this, the composition is also changed with increased concentrations of sodium, chloride, calcium and protein and a decrease in bicarbonate.[12]

Antibodies are found in saliva. Secretory IgA does not fix complement, but appears able to agglutinate bacteria, making them more readily phagocytized. Some investigators have found elevated levels of IgA in caries-resistant patients, while others have not.[13,14] Small amounts of IgG and IgM are also present, and raised levels have been found in patients with periodontitis or oral candidiasis. However, patients with hypogammaglobulinemia do not have an increased incidence of caries or gingivitis,[15] so the practical significance of these antibodies is uncertain.

Lysozymes are found in the saliva of all major glands They are formed or concentrated in the basal cells of the striated ducts. The lysozymes from different glands have different structures, but all act as a muramidase by hydrolyzing glycopeptides containing muramic acid in bacterial cell walls.[16] Lactoferrin is an iron-binding protein in saliva that may inhibit bacterial growth by denying them iron.[17] Lactoperoxidase with hydrogen peroxide and thiocyanate ion (the so-called thiocyanate-dependent factors) can inhibit lactobacillus, cariogenic streptococci and, perhaps, coliforms.[18] There is disagreement about the existence of

TABLE 3.—*Causes of Xerostomia*

Cause	*Incidence*
Local	
Candidiasis	6
Miscellaneous	6
Systemic	
Sjögren's syndrome	35
Drugs	25
Anemia	6
Endocrine	3
Idiopathic	19

TABLE 4.—*Changes in Saliva in Disease*

Variation From Normal	*Salivary Flow and Composition*
Dehydration, fatigue, infection, psychopathic emotional states, use of tranquilizers	↓ flow rate
Cigarette smoking, schizophrenia, acute stomatitis, heavy metal poisoning, rabies, pernicious and iron-deficiency anemia	↑ flow rate
Primary aldosteronism	↓ sodium, normal potassium
Cushing's disease	↓ sodium, normal potassium
Addison's disease	↑ sodium, normal potassium
Pregnancy	↓ sodium, ↑ potassium
Cystic fibrosis	↑ calcium, protein, amylase
Hyperparathyroidism	↑ calcium, phosphorus
Essential hypertension	↓ sodium and flow rate
Sarcoidosis	↓ amylase, kallikrein ↑ albumin, lysozyme
Acute pancreatitis	↑ amylase
Alcoholic cirrhosis	↑ potassium, amylase, flow rate
Irradiation	↑ sodium, chloride, calcium, protein ↓ bicarbonate

↓ = decreased, ↑ = increased

a bacteriolytic substance in the saliva of caries-free persons.[19-21] A substance named nerve growth factor exists in saliva that greatly stimulates nerve tissue growth. Its level has been reported to be raised in the serum of children with neuroblastoma.[22]

Changes in Saliva in Disease

Dehydration, admission to hospital, mental stress, psychopathic emotional states, fatigue, infection, raised ambient temperature, tranquilizers, ganglionic blockers and light deprivation decrease salivary flow. Cigarette smoking, acute stomatitis, heavy metal poisoning, acrodynia, rabies and the ingestion of highly seasoned foods increase flow. Chewing on one side of the mouth increases the flow on that side.

Xerostomia may be primary or secondary, and the causes are numerous. It is usually not a problem until the flow rate is less than 0.2 ml per minute per gland. In addition to the previously mentioned causes, pernicious and iron-deficiency anemia and loss of salivary tissue (as from irradiation, infection or Sjögren's syndrome) cause decreased flow. Most causes of xerostomia are systemic in nature, but a significant percentage are idiopathic (Table 3).

Many diseases affect salivary composition (Table 4). Primary aldosteronism causes a decreased sodium level with normal potassium content. It has been suggested that a sodium-potassium ratio of 0.3 or less is diagnostic, below 0.5 is suggestive and above 1.0 rules out aldosteronism (normal, 1.3).[23] Low sodium-potassium ratios are also found in Cushing's disease with a mean ratio of 0.5.[24(p115)] High ratios occur in Addison's disease with a mean ratio of 5.0. In pregnancy, the submandibular calcium concentration is reduced, whereas the sodium concentration is reduced and the potassium concentration is increased in both parotid and submandibular saliva.[25]

The salivary glands, like the other exocrine glands, are affected by cystic fibrosis. The submandibular saliva is thickened by increased amounts of calcium and calcium-precipitable proteins, with no change in viscosity.[26] Total protein, amylase, lysozyme and glycoprotein concentrations are increased in submandibular but not in parotid saliva.[27] There is no change in the flow rate in the major glands,[28] but there is a significant reduction in the minor glands.[29]

Thyroid diseases and their treatment may affect the saliva. The salivary glands concentrate iodine to 40 times the plasma level, regardless of the thyroid-stimulating hormone level or the state of thyroid function.[30] Hyperparathyroidism causes an increased amount of calcium and phosphorus in saliva, with the levels paralleling the parathormone levels.[31] In cases of essential hypertension, the sodium concentration and the flow rate are decreased.[32] In sarcoidosis, amylase and kallikrein levels are decreased, whereas albumin and lysozyme concentrations are increased.[33,34] Acute pancreatitis may cause an increase in the amount of amylase. Alcoholic cirrhosis may cause an increased flow rate with increased concentrations of potassium and amylase.[35] Salivary flow rate is decreased by depression and increased by schizophrenia.[36]

Inflammatory lesions may cause changes in saliva. In acute infections, the sodium and potassium levels approach those of serum.[37] There is also a pronounced decrease in phosphate concentration. Other elements that are increased in amount include glucose, IgA, IgG, IgM, albumin and transferrin, which leak from plasma, and myeloperoxidase, lactoferrin and lysozyme, which are produced by the inflammatory infiltrate. IgG dominates the immunoglobulins, reflecting the normal serum pattern rather than the normal salivary pattern, in which IgA dominates.

Irradiation causes pronounced changes in saliva, the most obvious being a severe reduction in flow rate. Flow rates are reduced 95% or more after full-course radiation therapy and this reduction persists indefinitely.[9,10] Histopathologic studies have shown that the parotid acini and the serous cells from the submandibular gland are severely injured, but there is little discernible change in the mucous cells. The composition is also altered, with increased amounts of sodium, chloride, calcium and protein and a decrease in bicarbonate. These changes lead to a significant rise in the number of dental caries.

Numerous systemically administered drugs can be detected in saliva, including iodide, heavy metals, thiocyanate, morphine, clindomycin and rifampin.[38] Digitalis toxicity causes greatly elevated levels of potassium and calcium, and this study can be used to distinguish between toxic and therapeutic doses.[39]

Inflammatory Disorders

Acute Suppurative Sialadenitis

Acute suppurative sialadenitis may involve the parotid or submandibular gland, with the vast majority of cases showing parotid involvement. The parotid gland is felt to be more susceptible because parotid saliva has less bacteriostatic activity than submandibular saliva.[10] Presumably this is because the bacterial aggregating ability—and thus eliminating ability—is greater with the high-molecular-weight glycoproteins in the mucous acini and the other antibacterial systems seem the same.[41]

Acute suppurative sialadenitis accounts for about 0.03% of hospital admissions.[40,42] About 30% to 40% of cases occur after an operation, with the highest incidence following gastrointestinal tract procedures, usually with an onset three to five days postoperative. The primary pathogenic event is thought to be salivary stasis, either from obstruction or from decreased production. Predisposing conditions include calculi, duct stricture, dehydration and poor oral hygiene. These conditions most frequently exist in an in-hospital patient who has reduced resistance and is receiving multiple medications that alter oral flora.[42] When, in addition, a patient is not eating, salivary flow is further reduced. An ascending bacterial infection occurs and leads to suppuration within the gland. This complication occurs in 1 in 1,000 to 2,000 operative procedures.

It occurs most frequently in the sixth and seventh decades, though it has been reported for all ages.[43] The sex distribution is equal.

The classic clinical presentation is a debilitated or postoperative patient in whom a diffuse enlargement of a parotid gland develops, with associated induration and tenderness. Purulent saliva can be expressed from the duct orifice and it occurs on both sides in 20% of cases.[44] A specimen of the purulent saliva should be cultured for aerobic and anaerobic bacteria and a Gram's stain done. The offending organism is usually coagulase-positive *Staphylococcus aureus*. Other occasionally implicated aerobic organisms include *Streptococcus pneumoniae, Escherichia coli* and *Haemophilus influenzae*.[45] Anaerobic organisms include *Bacteroides melaninogenicus* and *Streptococcus micros*.[46] On microscopic examination there is glandular destruction with abscess formation and erosion of the ducts with penetration of the exudate into the parenchyma.

Initial treatment consists of adequate hydration, good oral hygiene, repeated massage of the gland and antibiotics given intravenously. While awaiting culture results, empiric administration of a penicillinase-resistant, antistaphylococcal antibiotic is advisable, if the Gram's stain shows Gram-positive cocci. Mortality rates approach 20%,[47] though much of this is probably because it occurs in already seriously ill patients. Therefore, if a response to the appropriate treatment regimen does not occur quickly, incision and drainage should be done. This is carried out by raising a parotid flap as for a parotidectomy and then, using a hemostat, making multiple openings into the gland, spreading the hemostat in the general direction of the facial nerve. Following this, a drain is placed over the gland and the wound closed. Successful needle aspiration guided by ultrasound has been reported, and the use of new computed tomographic (CT) scanners should be equally feasible.

Chronic Recurrent Sialadenitis

The primary pathogenic event in chronic sialadenitis is believed to be a decreased secretion rate with subsequent stasis. Two theories of initiation are currently espoused. One is that repeated acute episodes or a single severe episode of suppurative sialadenitis leads to ductal metaplasia to mucus-secreting glands. This leads to an increased mucous content in the saliva, which contributes to the salivary stasis. The other theory is that if a gland is colonized by pyogenic bacteria, an acute suppurative infection will result, whereas colonization with opportunistic oral flora will lead to chronic, recurrent sialadenitis.

This disease is much more common in the parotid gland, presumably because of its longer, narrower duct,[48] making it more susceptible to stasis. Regardless of the cause, as time passes, the disease leads to sialectasis, ductal ectasia and progressive acinar destruction with an associated lymphocytic infiltrate. The lymphocytic infiltrate is a response to ductal and acinar damage, with progressive replacement of secreting glandular elements by the infiltrate.

This progressive glandular destruction causes several changes in the chemistry of saliva. There are increased amounts of sodium and protein[49(p344)] with a pronounced decrease in phosphate level. Also increased are IgA, IgG, IgM, albumin, transferrin, myeloperoxidase, lactoferrin and lysozyme. The IgG dominates the immunoglobulins, reflecting the serum pattern rather than the usual salivary pattern in which IgA dominates.

Clinically there is recurrent, mildly painful parotid enlargement, usually associated with eating. Physical examination confirms this, and massage of the gland often produces scanty saliva. In 80% of patients permanent xerostomia develops. Treatable predisposing factors, such as a calculus or a stricture, should be investigated and, if found, treated appropriately. If none is found, treatment should otherwise be conservative, involving the use of sialagogues, massage and administration of antibiotics during acute suppurative exacerbations. If conservative measures fail—and this is unusual—other treatment options include periodic ductal dilatation, ligation of the duct, total gland irradiation, tympanic neurectomy and excision of the gland. All of these options, except the last, work occasionally, but not uniformly. Ligation of the duct may successfully cause atrophy of the gland but sometimes results in an acute infection or in a mucocele. Irradiation produces an initial acute inflammatory reaction, but continued treatment results in destruction of the gland. This should only be considered in older patients, in whom the risk of irradiation-induced carcinoma is reduced. If all else fails, excision of the gland is curative.[50]

Recurrent parotitis may also occur in children. Unlike the adult form, this entity afflicts more male children than female children. The underlying cause is unproved, but the disease begins with the sudden onset of either unilateral or bilateral parotid swelling. Attacks may be single or recurrent, with varying degrees of enlargement during and between acute episodes. Saliva may be clear or flocculent and the flow rate decreased. Salivary chemistry levels are altered, as in adult patients.

Clinically an affected child is usually not ill, though there may be a mild rise in the temperature and the leukocyte count. Mild pain may be present, but a child will not have xerostomia.[51] The disease may disappear at puberty or continue into adulthood.

Benign Lymphoepithelial Lesion

The benign lymphoepithelial lesion belongs in a spectrum of diseases characterized by a lymphoreticular infiltration into the gland, combined with acinar atrophy and ductal metaplasia ending in the epimyoepithelial island.[52] Histologically there is chronic inflammation, with variations being related only to distribution and severity. Some regard this lesion as "end-stage" chronic recurrent parotitis. Other diseases within

this spectrum include primary and secondary Sjögren's syndrome. Unlike these, however, the benign lymphoepithelial lesion usually affects only a single salivary gland and is less predominant in women.

The usual clinical feature is asymptomatic enlargement of a single salivary gland. Superimposed infection may occur and should be treated as an acute sialadenitis. If the lesion is asymptomatic and is not cosmetically objectionable, no treatment is necessary.

Of considerable concern are occasionally seen benign lymphoepithelial lesions that evolve into more aggressive lesions. As of 1980, there had been reported evolution of the disease into 84 cases of lymphoproliferative disease, 27 cases of carcinoma and 12 cases of pseudolymphoma. The lymphoproliferative disorders are virtually all histiocytic or lymphocytic lymphoma involving extrasalivary sites. The sudden development of hypogammaglobulinemia or leukemia may herald the onset of lymphoma. The carcinoma is usually salivary and usually anaplastic. Many patients have been of Indian or Eskimo extraction, but this may represent merely a reporting artifact. These entities should be watched for and treated early and aggressively when they occur.

Sjögren's Syndrome

Sjögren's syndrome is characterized by a lymphocyte-mediated destruction of the exocrine glands leading to xerostomia and keratoconjunctivitis sicca. It is the second most common autoimmune disease after rheumatoid arthritis.[53] The average age by onset is 50 years and 90% of cases occur in women.

The clinical manifestations were first described by Hadden in 1888.[54] Four years later, Mikulicz published a single case report of a patient with bilateral lacrimal, parotid and submandibular gland swelling.[55] In 1933 Sjögren, a Swedith ophthalmologist, published a classic monograph on the disease, emphasizing its systemic nature.[56] Sjögren's syndrome occurs in two forms—primary, which involves exocrine glands only, and secondary, which is associated with a definable autoimmune disease, usually rheumatoid arthritis.[57]

Sjögren's syndrome generally runs a relatively benign course of primarily exocrine gland dysfunction. This leads to burning oral discomfort and a "sandy" sensation in the eye. Either unilateral or bilateral salivary gland swelling, usually involving the parotid, occurs in 80% of primary and 30% to 40% of secondary cases. The swelling may be intermittent or permanent. Arthritis is the most frequent initial symptom in secondary Sjögren's. Recent studies have shown that there are genetic differences between primary and secondary Sjögren's syndrome.[58,59]

Associated symptoms are numerous and include interstitial pneumonitis, dryness of the skin, Raynaud's phenomenon, achlorhydria, hepatosplenomegaly, genital dryness, hyposthenuria, myositis and pancreatitis. Patients with primary Sjögren's have a greater incidence of recurrent parotitis, Raynaud's phenomenon, purpura, lymphadenopathy, myositis and renal involvement than do those with secondary Sjögren's.[60]

TABLE 5.—*Autoantibodies in Sjögren's Syndrome*

Autoantibody	*Incidence Percent*
Rheumatoid factor	70-90
Antinuclear antibody	55-70
Salivary duct antibody	65
Parietal cell antibody	27
Thyroglobulin antibody	18
Thyroid microsomal antibody	21

TABLE 6.—*Sialochemical Values in Sjögren's Syndrome*

Parameter	*Sjögren's*	*Controls*
Flow rate (ml/min)	0.17	0.58
Sodium (mEq/liter)	65.0	23.0
Chloride (mEq/liter)	64.0	23.0
Potassium (mEq/liter)	20.0	22.0
Phosphate (mEq/liter)	2.3	6.3
Calcium (mEq/liter)	1.9	2.1
Urea (mEq/liter)	9.8	10.5
Total protein (mg/dl)	252.0	236.0
IgA	5.8	3.6
IgG	1.0	0.5
Albumin	1.3	0.8
Amylase (units/ml)	1,480.0	1,440.0

A number of laboratory findings suggest that one of the underlying defects in Sjögren's syndrome is B-cell hyperreactivity, with or without abnormalities of immunoregulation. These include polyclonal hypergammaglobulinemia, numerous autoimmune antibodies—both organ- and nonorgan-specific—and circulating IgG immune complexes.[61,62] The relative frequency of some antibodies is shown in Table 5. In addition, elevated levels of antibody to secretory IgA have been reported.[63]

Sialographic abnormalities parallel the clinical and histological severity of the disease, with a characteristic finding being one of varying degrees of sialectasis. Grossly and histologically the individual salivary gland resembles a gland involved with chronic inflammation. There is ductal ectasia on sialography and lymphoreticular infiltration, acinar destruction and the formation of epimyoepithelial islands. The lymphoreticular infiltration consists largely of small or medium-sized lymphocytes and plasma cell on electron microscopy.[64] Sialochemical studies have shown a number of abnormalities (Table 6). Sodium and chloride concentrations are about three times normal, whereas the phosphate level is one-half normal.[65] The potassium content is usually normal, as is the case in chronic inflammatory disorders. The amylase and total protein concentrations are normal, suggesting that the remaining acinar cells are capable of normal protein synthesis. The greatly reduced flow rate, however, markedly reduces the amount of antibacterial material delivered to the oral cavity. Dental caries are significantly increased.[66]

Sjögren's syndrome, like the benign lymphoepithelial lesion, is associated with an increased incidence of lymphoma. The incidence is increased 44 times over

TABLE 7.—*One Formula for Artificial Saliva*

Reagent	*Volume Grams*
Potassium chloride	2.398
Sodium chloride	3.462
Magnesium chloride	0.235
Calcium chloride	0.665
Potassium phosphate	3.213
Potassium dihydrogen phosphate	1.304
Methyl *p*-hydroxybenzoate	8.0
Flavoring	16.0
70% Sorbitol	171.0
Carboxymethylcellulose sodium	40.0
Sodium fluoride	17.68
FD&C red 40 dye (2%)	1.0 ml
Water q.s. add	4,000.0 ml

the normal and is usually of the histiocytic or mixed histiocytic-lymphocytic type.[67] Half of those in whom a lymphoma develops have had prior irradiation to the parotid. Pseudolymphoma may also occur and, like the lymphoma, has been shown to be of B-cell origin. Sjögren's syndrome has also been associated with biliary cirrhosis, other liver abnormalities, involvement of the larynx, the development of membranous glomerulonephritis, autoimmune liver disease and secondary amyloidosis.[68(p64)]

Treatment is symptomatic. Xerostomia causes a burning oral discomfort, difficulty in eating dry foods and decreased taste sensitivity. Mucosal ulcerations and increased dental caries may occur. The simplest treatment is the use of an artificial saliva swirled in the mouth and swallowed every three to four hours. (Table 7). The salivary glands should be stimulated to produce what saliva they can. Dental hygiene must be impeccable. Acute infections should be treated as acute sialadenitis.

Xerophthalmia is best treated with artificial tears every three to four hours as needed. Taping the lids closed at bedtime is an excellent precaution. Occasionally tarsorrhaphy may be necessary. Care must be taken as corneal ulcerations and perforations have been reported.[69] Patients also have an increased incidence of otitis media, bronchitis, pneumonia, pancreatitis and atrophic gastritis, which should be watched for and treated appropriately.

It has been suggested that an inadequate synthesis of prostaglandin E_1 is the key factor in xerostomia and xerophthalmia, and some success in raising tear and saliva production has been reported by raising the level of prostaglandin E_1 precursors and vitamin C in the diet.[70]

Granulomatous Diseases

Primary tuberculosis of salivary tissue is uncommon. The parotid is most commonly involved, usually on one side only. The infection is felt to arise usually from the tonsils or teeth. It occurs in one of two forms—an acute inflammatory lesion or a chronic tumorous lesion. The former may be a difficult diagnostic problem and the diagnosis may not be made until, faced with a lack of response to conventional antibiotics, acid-fast salivary stain and purified-protein derivative (PPD) tests are done. The PPD may be unreliable as infections caused by atypical mycobacteria are increasing relative to *Mycobacterium tuberculosis hominis*.[71] Treatment is as for any acute tuberculous infection. The chronic tumorous form is usually diagnosed only after excision of the gland for a suspected tumor. This may change with the more widespread use of fine needle aspiration cytologic studies. Excision is curative. Secondary tuberculosis can occur and more commonly involves the submandibular and sublingual glands.

Animal scratch disease may involve the salivary glands, but only by contiguous spread from a lymph node. This is a self-limiting disease and treatment is symptomatic.

Actinomycosis may also occur in the salivary glands. As with actinomycosis elsewhere, treatment involves incision and drainage combined with long-term penicillin therapy.

Sarcoidosis is a granulomatous disease of cryptogenic cause that is a diagnosis of exclusion. Whereas salivary gland involvement occurs in 33% of cases in histologic studies, it is clinically manifest in only 6%.

Uveoparotid fever (Heerfordt's syndrome) is a particular form of sarcoidosis consisting of uveitis, parotid swelling and facial paralysis. It usually occurs in the third or fourth decade and has a prodrome of fever, malaise, weakness, nausea and night sweats lasting several days to several weeks. This may occur with or without other systemic signs of sarcoidosis. Generally both parotids enlarge simultaneously, and submandibular, sublingual and lacrimal involvement may occur. The swelling lasts months to years without suppuration and with eventual resolution. Involvement of the minor salivary glands may occur, and labial biopsy may establish the diagnosis.[72] The sialographic appearance depends on the extent of glandular invasion and ranges from normal to moderate loss of ductal radicals. Scanning using technetium Tc 99m frequently shows abnormalities. Histologic examination shows the expected noncaseating granulomas, which, like tuberculosis, involve the lymphoid tissue more than the parenchyma. Sialochemistry studies show a decreased level of amylase and kallikrein, with an increase in albumin and lysozyme levels. Treatment is symptomatic. with corticosteroids being most useful in the acute phase, particularly for facial paralysis. Even without treatment the facial paralysis is usually transient. Uveitis should be followed closely as it can lead to glaucoma.

Viral Infections

Mumps is by far the most common cause of parotid swelling and is the most common viral agent to involve the salivary glands. It is most commonly recognized in the 4- to 6-year-old age group. The incubation period is two to three weeks, with a clinical onset characterized by pain and swelling in one or both parotids. Systemic symptoms include fever, malaise,

myalgias and headache, and usually resolve before the parotid swelling. Many cases are subclinical, and studies have shown that more than 95% of adults have neutralizing antibodies.[73] A recent epidemiologic study has shown a statistically significant association between mumps and the subsequent rapid onset of childhood diabetes.[74]

Salivary gland inclusion disease is a rare form of cytomegalic inclusion disease. It involves newborns and may cause mental and physical retardation as well as hepatosplenomegaly, jaundice and thrombocytopenic purpura. Other viral agents that may infect the salivary glands include coxsackievirus A, echovirus, influenza A and the virus of lymphocytic choriomeningitis. The treatment in all cases is directed toward symptoms.

Noninflammatory, Nonneoplastic Disorders

Sialolithiasis

Of all salivary calculi, 80% occur in the submandibular gland, whereas less than 20% occur in the parotid and 1% occur in the sublingual gland. Minor salivary gland calculi are uncommon and have a predilection for the upper lip and buccal mucosa.[75]

For the major glands, there is a single calculus in 75% of cases and multiple gland involvement in 3%. Most occur in middle age and there is a slight male predominance. Calculi may occur unassociated with other salivary disease, but also occur in two thirds of cases of chronic sialadenitis. The only systemic disease associated with salivary calculi is gout, and the calculi are then composed of uric acid.

Most calculi are composed largely of calcium phosphate as the hydroxyapatite, with small amounts of magnesium, carbonate and ammonium. The organic matrix is composed of various carbohydrates and amino acids. About 90% of submandibular calculi are radiopaque, but 90% of parotid calculi are radiolucent. Prerequisites for calculus formation are stasis and a nidus of material for the precipitation of salivary salts. There is some evidence that most submandibular calculi arise de novo around a nidus of mucus, whereas parotid calculi are preceded by an inflammatory response and form around inflammatory cells.[76] The submandibular gland is believed to be more susceptible because its saliva is more alkaline, has a greater concentration of calcium and phosphate and has a higher mucus content. In addition, the duct is longer and the flow is antigravity.

Occasionally calculi are asymptomatic or appear as acute suppurative sialadenitis. Usually a patient has had recurrent swelling and pain in the involved gland, usually aggravated by eating. With repeated episodes, infection may intervene. In general, sialoliths within the glandular parenchyma are associated with less severe symptoms than those producing obstruction of the main duct. On physical examination diffuse enlargement and tenderness of the involved gland are found. A calculus is frequently palpable. Calculi within a major duct tend to be smooth, whereas those within the gland tend to be irregular. Massage of the gland shows decreased flow of cloudy, sometimes mucopurulent saliva. For the usual submandibular gland radiopaque calculus, routine mandibular roentgenography suffices for the diagnosis. For parotid calculi, an anteroposterior roentgenogram coupled with an intrabuccal film show a calculus 71% of the time.[77] For either gland, sialography is essentially 100% effective. Ultrasonography may also be used.[78]

Complications of sialolithiasis include acute suppurative sialadenitis and ductal ulceration and stricture. Treatment depends on the location of the calculus; if it is near the duct orifice, intraoral removal is simple and curative. If the calculus is within the hilum of the submandibular gland, complete excision of the gland is curative and is done when symptoms are unacceptable or when frequent infections occur. For the parotid gland also, an attempt at conservative therapy is prudent. If recurrent infections occur, however, a parotidectomy should be done. In cases in which only the calculus is removed, the recurrence rate may be as high as 18% because the underlying cause, which is unknown, has not been corrected.

Cystic Lesions

True cysts of salivary tissue are unusual and most occur in the parotid, where they account for 2% to 5% of all parotid lesions. Cysts may be congenital—of which there are three types—or acquired. The dermoid cyst consists of keratinizing squamous epithelium with associated skin appendages and is treated by complete removal with preservation of the facial nerve. The congenital ductal cyst is generally seen in infancy. No therapy is required unless repeated infections occur.[79]

Cysts of the first branchial groove account for less than 1% of all branchial arch anomalies. There are two types: type I is ectodermal and is a duplication anomaly of the membranous external auditory canal; type II is ectodermal and mesodermal and is a duplication anomaly of the membranous and cartilaginous external auditory canal. A type I cyst typically occurs posterior, inferior or anterior to the ear and may bear any relationship to the facial nerve. Prior infection, with or without incision and drainage, may mask the true nature of the lesion. Complete excision during a quiescent period, with preservation of the facial nerve, is curative. A type II lesion may occur from the preauricular area to the hyoid bone. Regardless of the location, the tract is intimately associated with the facial nerve. Again, frequent prior infections may obscure the true lesion. As with type I lesions, excision during a quiescent period, with preservation of the facial nerve, is curative.

Acquired cysts may be due to neoplasms, a benign lymphoepithelial lesion, trauma, parotitis, calculi, duct obstruction or mucus extravasation.[80] Further, the presence of a cyst does not preclude the possibility of a neoplasm, especially a pleomorphic adenoma, an adenoid cystic carcinoma, a mucoepidermoid carcinoma or papillary adenocystoma lymphomatosum (War-

TABLE 8.—*Nonneoplastic, Noninflammatory Causes of Salivary Enlargement*

Nutritional Deficiency
Hypoproteinemia
Pellagra
Beriberi
Hypovitaminosis A
Generalized malnutrition
Obesity
Metabolic or Endocrine Abnormalities
Any malabsorption disorder
Pregnancy
Lactation
Menopause
Diabetes mellitus
Hypothyroidism
Testicular atrophy
Uremia
Alcoholic cirrhosis
Other
Drugs
Pneumoparotitis
Sialodochitis fibrinosa (Kussmaul's disease)

thin's tumor). These are the neoplasms most commonly cystic and are the most common salivary gland neoplasms. For an acquired cyst with an identifiable underlying cause, the latter should be treated first. If that fails, the cyst should be excised. Mucoceles and mucus-retention cysts usually involve the minor salivary glands and most commonly occur in the lips, buccal mucosa and ventral tongue. Mucus-retention cysts are true cysts with an epithelial lining and result from partial duct obstruction. Complete duct obstruction leads to glandular atrophy.[81] Mucoceles do not possess an epithelial lining and are not true cysts. Instead they represent mucus extravasation into the soft tissue. Treatment is by excision or marsupialization if treatment is required. A simple ranula is a mucus-retention cyst of the sublingual gland.

Trauma

Direct injuries of note usually involve a penetrating injury that lacerates the parotid duct. Any penetrating injury to the cheek posterior to the anterior border of the masseter muscle should be suspected of causing a duct injury. If the duct cannot be identified in the wound, a probe should be passed into the duct transorally and located in the wound. This should allow assessment of the duct. If the duct has been transected, the optimum treatment is immediate end-to-end anastomosis over a polyethylene catheter with size 9-0 sutures. The catheter is sutured in place to the buccal mucosa and removed in two weeks. If the proximal end of the transected duct cannot be readily identified, the wound should be carefully dried and the gland compressed. This will often produce enough saliva from the cut end of the duct to allow its identification. If primary anastomosis is impossible but the proximal duct is long enough, the duct may be sutured directly to the buccal mucosa through a puncture wound. If the proximal duct is too short, it may be ligated. This will usually lead to atrophy of the gland, although infection or a salivary-cutaneous fistula may result.

Occasionally a duct injury is missed only to become manifest several days later as a swelling below a sutured wound. In this situation, the wound must be opened and the duct identified and repaired.

Laceration of the parenchyma, in isolation, can usually be managed conservatively. Generally, merely closing the parenchyma and capsule with a few interrupted sutures will suffice. A salivary-cutaneous fistula may develop, but will usually heal with repeated aspiration and a pressure dressing. Resolution often takes 7 to 14 days, by which time the traumatized ductal system will have reopened. Persistence of a fistula strongly suggests duct obstruction in addition to the parenchymal injury.[82] Sialography should be done to investigate this. If ductal obstruction is found, repair should be carried out if possible. If not possible and the fistula persists, a tympanic neurectomy may help. Occasionally a salivary-cutaneous fistula can be diverted into the oral cavity. The entire fistulous tract is excised, turned into the oral cavity through the cheek and sutured to the buccal mucosa.[83] If that fails, excision of the gland or irradiation to destroy the gland may be carried out. Sometimes a sialocele develops instead of a fistula, which may occur in the absence of penetrating trauma.[84]

Penetrating injuries may also transect one or more branches of the facial nerve. The facial nerve of any patient who has suffered a penetrating injury to the face should be thoroughly evaluated. If the wound is anterior to a vertical line from the lateral canthus to the mental foramen (a line approximating the anterior border of the masseter muscle) and only a single branch is involved, repair is probably unnecessary. In this instance recovery is likely from distal anastomosing branches. Posterior to this line, repair should be done immediately.

Blunt trauma can also cause contusion, edema or hemorrhage of the gland. Contusions and edema usually resolve without treatment, though temporary duct obstruction may occur. A hematoma, if significant, should be drained before it becomes organized. If not, subsequent fibrosis and scarring may lead to duct obstruction as well as to cosmetic deformity.

In general, injuries to the submandibular or sublingual glands are managed in the same way as those to the parotid. Penetrating injuries other than parenchymal laceration are uncommon because of the protection offered by the mandible. If an injury does not heal satisfactorily, the gland should be excised.

Sialadenosis

Sialadenosis is a nonspecific term used to describe a noninflammatory, nonneoplastic enlargement of a salivary gland, usually the parotid. Some of the causes are listed in Table 8. Salivary gland enlargement is usually asymptomatic.

Bilateral parotid swelling is common in obesity. A complete endocrinologic and metabolic workup should

be done before a diagnosis of fatty hypertrophy is made. This is because obesity is frequently associated with other disorders such as diabetes mellitus, hypertension, hyperlipidemia and menopause. In particular, hypertrophy is frequently associated with diabetes mellitus and has been reported in cases of acromegaly.

Malnutrition is also frequently associated with sialadenosis, but it is also associated with pellagra, cirrhosis, diabetes mellitus and beriberi.[85] In such cases the level of proteinemia is usually from 3 to 6 grams per dl. Sialadenosis has been reported in cases of kwashiorkor (literally, "red boy") and hypovitaminosis A.[86(p321)] The swelling in these conditions is due to acinar hypertrophy.

The association of parotid swelling with alcoholic cirrhosis is well recognized. It is so rare in cases of nonalcoholic cirrhosis that it can be used as a differential diagnostic feature.[87] In alcoholic cirrhosis, parotid enlargement occurs in 30% to 80% of cases. Current evidence suggests the enlargement is based on protein deficiency, and the histologic changes are similar to those seen in malnutrition. In these patients, the salivary output is normal, but the amylase concentration is increased.

As already implied, any disease that disrupts gastrointestinal absorption of nutrients may lead to parotid hypertrophy. Reported diseases include celiac disease, bacillary dysentery, carcinoma of the esophagus, Chagas's disease and ancylostomiasis.[88] Sialadenosis may occur in cases of uremia, hypothyroidism, myxedema, testicular or ovarian atrophy, pregnancy, lactation and chronic relapsing pancreatitis.

The prognosis of sialadenosis is usually good. The parotid glands generally revert to normal following correction of the underlying cause.

Other Noninflammatory, Nonneoplastic Disorders

Thiourea, isoproterenol, methimazole, phenylbutazone, phenothiazine, thiocyanate, iodine compounds and heavy metals may cause salivary gland enlargement.

Pneumoparotitis may result from any factor that increases intrabuccal pressure. It has been reported in glass blowers, following intubation or endoscopy and as an idiopathic event.

Sialodochitis fibrinosa (Kussmaul's disease) consists of a mucus plug obstructing a collecting duct. This usually occurs in a dehydrated patient and occurs as recurrent swelling with associated pain. The appearance of a mucus plug at the duct orifice is diagnostic. Treatment consists of gentle massage and sialagogues to extrude the plug, in addition to rehydration where appropriate.

Occasionally attention is directed to the salivary glands because of uncontrolled drooling. This generally occurs in neurologically damaged patients. A number of treatments have been advocated. Good results have been reported with bilateral tympanic neurectomy and with submandibular duct relocation. Satisfactory results have also been reported with parotid duct relocation. A more aggressive approach consists of relocating both parotid ducts combined with excising both submandibular glands. In general, drooling should be treated in a progressive manner, with each additional procedure indicated only by failure of the preceding procedure. Radiation should be reserved for operative failures to avoid side effects of xerostomia and increased dental caries, which can be significant management problems in themselves in these patients.

Cheilitis glandularis is an uncommon disease characterized by enlarged labial salivary glands, which secrete a clear, thick, sticky mucus.[89] The glandular hypertrophy may cause eversion of the lower lip. Vermilionectomy is generally curative.

Necrotizing sialometaplasia is a disease of cryptogenic origin, although some cases appear to occur as a reaction to injury. It generally begins as a mucosal ulceration in the hard palate, but may occur anywhere salivary tissue is found. There is a male predominance. It was first reported in 1973,[90] and its importance lies in the fact that it can be mistaken for squamous cell or mucoepidermoid carcinoma clinically and histologically. The lesion is always self-healing and requires no treatment other than biopsy.

Neoplasms

A thorough discussion of neoplasms is beyond the scope of this article. Briefly, salivary gland neoplasms represent less than 3% of all tumors. In all, 75% to 85% occur in the parotid; 80% of parotid, 65% of submandibular, 50% of minor salivary gland and 20% of sublingual gland tumors are benign. There is no significant sex distribution in whites, but nonwhite women have an increased incidence over nonwhite men.

Most benign and malignant tumors appear as an asymptomatic mass below intact skin or mucosa. The growth rate varies and 80% of parotid tumors arise in the caudal aspect of the superficial lobe. Thus every subcutaneous mass in the region of the inferior attachment of the ear should be considered a probable parotid neoplasm.

The basic treatment of benign tumors is complete excision with a cuff of normal tissue around the tumor. For parotid tumors, this means parotidectomy with preservation of the facial nerve.

The behavior of salivary neoplasms was best described by Ackerman and del Regato: "The usual tumor of salivary gland is a tumor in which the benign variant is less benign than the usual benign tumor and the malignant variant is less malignant that the usual malignant tumor."[91] Therefore treatment programs are best evaluated after 20 years rather than five or ten years. For instance, it was once felt that distant metastasis from malignant salivary tumors was uncommon. It is now clear that as the length of follow-up increases, so does the incidence of distant metastasis. The lungs are the most common site, followed by the bones.

The only known risk factors for malignant salivary

tumors is prior irradiation[92] and prior breast cancer in women.[93]

The treatment of malignant salivary neoplasms depends on the histologic type and the clinical stage at presentation. The general tendency at present is to do less aggressive surgical procedures, combined with a more liberal use of postoperative irradiation. Irradiation alone is never the optimum treatment choice.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Hyperthermia Treatments for Cancer

QUESTION:

Are hyperthermia treatments for cancer considered accepted medical practice or are they investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Internal Medicine, Otolaryngology/Head and Neck Surgery and Radiology, hyperthermia remains an investigational treatment for cancer. Several studies in animals and in humans have shown that hyperthermia may be associated with cancer regression, particularly in the treatment of superficial neoplasms. However, the safe application of hyperthermia, the use of local versus systemic heating techniques and the combination of hyperthermia with other antitumor modalities, such as radiotherapy and chemotherapy, require further investigation. There are no clear indications for hyperthermia as a standard modality in conventional cancer treatment.

Though it may prove to have practical application in the future, hyperthermia treatment for cancer should be conducted under research protocols in centers where the resources exist to properly evaluate the results of this therapy. Research is now being done at a number of institutions in the United States.

Specialty Conference

Intestinal and Liver Toxicity of Antineoplastic Drugs

Discussants

GEORGE B. McDONALD, MD, *and* NIGENDRA TIRUMALI, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Assistant Professor of Medicine, and Philip J. Fialkow, Professor and Chairman of the Department of Medicine.

GEORGE B. McDONALD:* The dosage of antineoplastic drugs is limited by toxic effects on the bone marrow, lungs, kidneys and gastrointestinal system. Although the gastrointestinal side effects of nausea, vomiting, anorexia, abdominal pain and diarrhea are usually self-limited, in some patients extensive intestinal ulceration, ileus, esophagitis, pancreatitis and liver failure may develop. The signs and symptoms of toxicity may be similar to those of the underlying malignancy and to those of intestinal and liver infections in an immunocompromised host. In this discussion the effects of antineoplastic drugs on the organs of the gastrointestinal system are reviewed, with emphasis on the more severe clinical consequences.

Oral and Esophageal Mucositis

Several drugs may cause sloughing of the mucosa of the mouth and tongue, resulting in oral pain and decreased food intake (Table 1). The degree of mucositis is related to the dose and schedule of chemotherapy and is more severe in patients who have received or are receiving radiotherapy.[1] Although drug-induced hypopharyngeal mucosal injury may produce pain on swallowing and a sensation of food sticking in the throat, esophageal symptoms are not common unless patients also receive thoracic radiation therapy.[2,3] Herpes simplex virus infections often occur in patients with chemotherapy-induced mucositis and may lead to more severe oral and esophageal symptoms.[4,5]

Some drugs, such as doxorubicin hydrochloride and dactinomycin (formerly actinomycin D), may potentiate radiation effects on squamous epithelium,[6] whereas others, including vinblastine sulfate, hydroxyurea and procarbazine hydrochloride, produce an additive toxic effect with irradiation.[7] Symptoms of retrosternal pain and painful swallowing are usually self-limited, but dense esophageal strictures have been reported.[8,9] Mucosal inflammation may be followed by abnormal motility, leading to poor acid clearing from the esophagus and dysphagia.[10] Diminished salivary flow may also follow chemotherapy and contribute to peptic esophagitis.[11]

It is important to distinguish chemotherapy- or irradiation-related mucosal toxicity from peptic esophagitis, infection and motility disorders. Fiberoptic endoscopy may be needed to make this distinction in patients who have severe or persistent pain and dysphagia. Empiric treatment with antireflux measures and antacids may be helpful for patients with chemotherapy-related esophageal symptoms but cimetidine should be used cautiously in neutropenic patients because of its marrow toxicity.[12]

Intestinal Toxic Reactions

Cellular Abnormalities

Multiple morphologic and functional abnormalities of intestinal absorptive cells have been described in animals and in people treated with antineoplastic drugs.[1,13] Antimetabolites inhibit DNA synthesis in rapidly proliferating crypt cells of the intestinal mu-

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TABLE 1.—*Gastrointestinal Tract Symptoms Associated With Antineoplastic Chemotherapy*

Symptoms	*Drugs*
Oral mucositis	Dactinomycin, bleomycin sulfate, cytarabine, daunorubicin hydrochloride, doxorubicin hydrochloride, 5-fluorouracil, methotrexate, vincristine sulfate
Dysphagia, heartburn	Dactinomycin, doxorubicin, hydroxyurea, procarbazine hydrochloride, vinblastine sulfate
Watery diarrhea	Dactinomycin, cisplastin, cytarabine, daunorubicin, doxorubicin, floxuridine, 5-fluorouracil, 6-mercaptopurine, methotrexate, mithramycin
Bloody diarrhea	High doses of antimetabolite drugs, sequential protocols using cytarabine
Constipation, ileus	Vinblastine, vincristine, vindesine
Abdominal pain	
From Enteritis	*See* Bloody diarrhea, above
From Pancreatitis	Prednisone, azathioprine, 6-mercaptopurine, L-asparaginase, estrogens, combination therapy
From Hypersensitivity reaction	L-Asparaginase, anthracycline antibiotics, busulfan, cisplatin
From Hepatic venocclusive disease	*

*See Table 2.

cosa, but these changes are usually not accompanied by serious clinical illness unless unusually high drug tissue concentrations are present or sequential drug protocols are used.[14] Ultrastructural alterations involving mitochondria, endoplasmic reticulum and Golgi apparatus have been found in intestinal absorptive cells of patients who received a single dose of methotrexate intravenously.[15] Single doses of methotrexate by mouth and combination chemotherapy with methotrexate, cyclophosphamide and 5-fluorouracil may also produce changes in ultrastructure.[13,16] However, in a prospective study of patients receiving combination chemotherapy no abnormalities in villous architecture were found, although crypt mitoses were decreased.[17]

Diarrhea

Despite the changes in intestinal mucosal cells caused by chemotherapy, many patients have only transient symptoms. Watery diarrhea may occur with many chemotherapeutic agents (Table 1), particularly when high-dose regimens are used.[1,18] Bloody diarrhea due to mucosal sloughing has been described after high-dose therapy with antimetabolite drugs (such as 5-fluorouracil) and several patients have died after inadvertent infusion of these and other drugs into arteries supplying the intestine or stomach.[13,19-21]

Mucosal Necrosis

Extensive mucosal necrosis associated with bloody diarrhea, abdominal pain and protein-losing enteropathy has been described in patients after sequential therapy with drug regimens that include cytarabine (cytosine arabinoside).[14,22] After the first week of therapy in these patients, only a single-cell layer of atypical epithelial cells remained; but, in patients who survived the initial destruction, mucosal regeneration was almost complete within two weeks unless infection supervened.[14] Intestinal infections with fungi and bacteria were common, leading to peritonitis, liver abscess, sepsis and pneumatosis cystoides intestinalis.[14] Other studies of combination chemotherapies that do not include cytarabine have not shown similar mucosal damage.[13,17] Synchronization of intestinal cell mitosis followed by administration of cytarabine may have been responsible for the extensive destruction seen in these patients.[14,22] There is greater sensitivity to cytarabine when intestinal cells are "frozen" in the S phase of mitosis.[23] Repair and clinical improvement may be rapid, however, with complete morphologic recovery within 10 to 20 days.[24,25]

Malabsorption

Malabsorption has not been a common finding in patients treated with intensive combination chemotherapy.[13,17] Absorption of D-xylose may be decreased during methotrexate therapy,[26] but normal absorption has been documented in patients receiving prolonged combination chemotherapy.[13,17] The ability of the intestine to absorb nutrients despite combination chemotherapy may be due to rapid repair of damage and the large functional reserve of the small bowel. Nutrients can be delivered to the small intestine by either a nasoduodenal or a jejunostomy tube if nausea and vomiting limit oral intake. For example, sterile food given by tube to patients undergoing intensive chemotherapy for acute leukemia prevented the weight loss and hypoalbuminemia found in a control leukemic group on a hospital diet.[27]

Constipation and Distention

In patients receiving antineoplastic drugs, constipation may result from diminished oral intake, opiates or anticholinergic medication. Neurotoxicity of *Vinca* alkaloids may lead to constipation and pseudo-obstruction of the intestine.[28,29] In patients with a neurotoxic reaction, crampy abdominal pain, constipation and distention may appear within days of vincristine sulfate infusion. Resolution usually occurs over several weeks. The syndrome is more common and severe with higher doses and in older patients; mortality is highest in patients with pseudo-obstruction.[30,31]

Intestinal Infections

The normal intestinal mucosa is an effective barrier to microbial invasion.[32] The effects of malignancy and antineoplastic drugs on this barrier are not well de-

TABLE 2.—*Hepatotoxic Manifestations of Antineoplastic Agents*

*Venocclusive Disease**	*Hepatocellular Necrosis*	*Hepatocellular Fatty Change*	*Cholestasis*	*Fibrosis*	*Peliosis Hepatis*	*Hepatic Neoplasms*
Mitomycin C	*Frequent*	L-Asparaginase	6-Mercaptopurine	Methotrexate	Androgens	Estrogens
6-Thioguanine	Mithramycin	Dactinomycin	Azathioprine	Azathioprine	Azathioprine	Androgens
Azathioprine	L-Asparaginase	Mitomycin C	Busulfan		Hydroxyurea	Methotrexate
Cytarabine	Streptozocin	Bleomycin sulfate	Amsacrine			
Dacarbazine	Methotrexate (high-dose)	Methotrexate				
Indicine-*N*-oxide (INO)						
Daunorubicin hydrochloride						
Combination chemotherapy	*Rare*					
Radiation therapy plus	Nitrosoureas					
Cyclophosphamide	6-Thioguanine					
Busulfan	Cytarabine					
Carmustine	Doxorubicin hydrochloride					
Mitomycin C	5-Fluorouracil					
Other regimens	Cyclophosphamide					

*Includes reports of predominant pericentral hepatocyte necrosis and congestion.

fined, but immunosuppression and granulocytopenia are common antecedents of intestinal infections with aerobic organisms and fungi.[33,34] Pseudomembranous colitis due to *Clostridium difficile* toxin has been associated with chemotherapy[35]; other toxin-producing organisms may also proliferate.[36,37] Cytomegalovirus can be a primary intestinal pathogen, causing esophagitis, intestinal ulceration, abdominal pain and diarrhea.[38-41] Candida infections can involve the esophagus, stomach and small bowel.[34,42,43] Parasite infestation in immunosuppressed patients is commonly due to *Giardia lamblia* and *Coccidia* sps.[44-47] Nonspecific symptoms such as fever, abdominal pain, diarrhea, vomiting and dysphagia should not be attributed to toxicity of antineoplastic drugs until infectious causes have been considered.

Hypersensitivity Reactions

Another toxic manifestation of antineoplastic drugs is abdominal cramping due to edema of the gut wall, which occurs as part of a more generalized hypersensitivity reaction.[48] Drugs that may produce these symptoms are listed in Table 1. Blockade of histamine receptors and pretreatment with glucocorticoids could be useful in preventing these reactions, but would not be effective in dealing with other causes of abdominal pain.

Toxic Reactions of Liver

NIGENDRA TIRUMALI, MD:* Critical evaluation of liver disease produced by antineoplastic drugs is difficult because cancer patients have many other causes of hepatic dysfunction, including metastasis, viral hepatitis, sepsis and concurrent use of other hepatotoxic drugs. A wide range of histopathologic changes has been attributed to antineoplastic drugs (Table 2), but fortunately serious hepatotoxic reactions are infrequent. Perhaps the liver is protected by its relatively slow rate of cell division and by its abundance of drug-inactivating enzymes.

Venocclusive Disease

Several antineoplastic drugs can cause obliteration of the central and sublobular veins of the liver (venocclusive disease), with resultant jaundice, hepatomegaly, abdominal pain, ascites and encephalopathy. Venocclusive disease was known to occur with high-dose radiation therapy[49] or the ingestion of pyrrolizidine alkaloids,[50] but it was only recently recognized as a toxic effect of antineoplastic drugs. Urethane-related liver failure due to venocclusive disease was described in the 1950s[51] and more recent reports suggest that several other agents may also cause this disease (Table 2).[52-60] It is especially common in patients who receive marrow transplants for malignancy.[61,62] Venocclusive disease has been reported in 20% of patients with leukemia who received a combination of antineoplastic drugs (usually cyclophosphamide) and total body irradiation (1,000 to 1,400 rads) in preparation for marrow transplantation.[62] The prevalence of venocclusive disease may be higher with conditioning regimens that use higher-dose chemotherapy, busulfan or dimethylbusulfan, carmustine (BCNU), or mitomycin C.[61,63-65] The histologic lesions of venocclusive disease have been seen in marrow transplant patients who showed no clinical sign of liver disease, suggesting that this disorder can occur in a mild form.[61]

Preexisting liver disease is an important risk factor for venocclusive disease. In a large series of patients with leukemia who received marrow transplants, pretransplant hepatitis was the most important predictor of venocclusive disease.[66] Thus, drugs that cause venocclusive disease or pericentral necrosis should be used with caution in patients with hepatitis. Similarly, when patients with hepatic metastasis receive palliative irradiation to the liver, concomitant chemotherapy should be used cautiously because of the risk of fatal venocclusive disease.[67-69]

The prevalence of venocclusive disease is much low-

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er among patients treated with antineoplastic drugs but without irradiation. The drugs listed in Table 2 have been incriminated as causes of venocclusive disease, though in many of these cases, the published histopathology shows pericentral hepatocyte necrosis and congestion without venular occlusion. The venular lesions of venocclusive disease are easily overlooked, and may be absent in the biopsy specimens because of sampling error.[61] Alternatively, some antineoplastic drugs may preferentially damage pericentral hepatocytes without causing venule damage.[70]

Many patients who have venocclusive disease due to antineoplastic drugs die of liver failure. However, in the case of marrow transplantation, about 50% of patients recover without clinical sequelae, usually within five weeks.[62] There is no known specific treatment for venocclusive disease. Management of these patients should include attention to sodium and water balance, encephalopathy and clotting abnormalities.

Drug-Induced Hepatitis

The agents listed under "Hepatocellular Necrosis" (Table 2) cause dose-related injury, except for cyclophosphamide, which has been reported to cause an idiosyncratic reaction. In most patients with drug-induced hepatitis, hepatic enzyme elevations are transient. Mithramycin produces early, often very high levels of lactic dehydrogenase and serum aspartate amino transferase (AST) in nearly all patients.[71] Jaundice is not a prominent feature, and the abnormal liver enzyme levels return to normal within a month after withdrawal of the drug. However, a bleeding diathesis may result from depression of coagulation factor synthesis by the liver. The pathologic lesions include hepatocellular necrosis, centrilobular congestion and fatty liver. The mechanism of mithramycin toxicity is related to diminished hepatic protein production through inhibition of DNA-dependent RNA synthesis.[71]

Hepatic dysfunction occurs in 50% to 75% of L-asparaginase-treated patients within a few days of the onset of therapy and resolves in a few weeks in most patients.[72-74] Impaired protein synthesis in the liver leads to decreased fibrinogen, ceruloplasmin, haptoglobin, transferrin and clotting factor levels in serum. Although prolonged prothrombin and partial thromboplastin times are seen, clinically significant bleeding is rare. Fatal hepatocellular failure has been reported. Histologic findings include variable necrosis with fatty infiltration.

Streptozocin, the most hepatotoxic of the nitrosoureas, causes transient serum AST elevations,[75,76] but fatal hepatotoxic reaction has not been reported. The histologic lesions have not been well defined, though hepatocellular necrosis has been noted in autopsy specimens. Carmustine also produces mild elevation of serum AST, alkaline phosphatase or bilirubin levels in up to 26% of patients.[77,78]

High-dose methotrexate may produce transient, reversible elevations of serum AST and bilirubin levels in many patients. No distinct hepatic lesions have been seen on autopsy specimens, however, even after 6 to 18 months of therapy.[79,80] Serious hepatocellular liver disease is uncommon with the other agents reported to cause hepatocellular necrosis.

Fatty Liver

Fatty infiltration of the liver can be produced by a number of agents (Table 2). Clinical manifestations are minimal but hepatomegaly and endocrine stigmata (spider nevi, gynecomastia, testicular atrophy) have been noted.[81]

Cholestasis

A cholestatic injury has been seen frequently in patients treated with 6-mercaptopurine.[82,83] Adults are affected more often than children.[84] Jaundice and modest AST elevations appear one to two months after initiation of therapy. The histologic findings include both intrahepatic cholestasis and parenchymal cell necrosis. If administration of the drug is continued, fatal hepatic failure can result. There have been reports of 6-mercaptopurine hepatotoxicity with concurrent administration of doxorubicin hydrochloride (adriamycin).[85]

The incidence of azathioprine-induced liver disease is lower than that of 6-mercaptopurine, but the clinical presentation is similar. Some investigators have suggested that patients in whom hepatic injury develops have a high rate of conversion of 6-mercaptopurine to azathioprine.[70]

Amsacrine (m-AMSA), an investigational agent used in the treatment of acute myeloid leukemia, produces mild jaundice in up to 30% of patients. A single case of fatal hepatotoxic reaction has been reported with the use of amsacrine.[86] Cholestatic jaundice that was probably an idiosyncratic reaction has been reported with the use of busulfan.[87]

Hepatic Fibrosis

Fibrosis and cirrhosis of the liver have been described following chronic low-dose administration of methotrexate in patients with psoriasis and in children with acute lymphocytic leukemia. The frequency of cirrhosis with daily intake of methotrexate by mouth has been as high as 24%, and increases when the cumulative dose is more than 2.4 grams.[88,89] The prevalence is higher in patients given frequent small doses of methotrexate than in those given larger doses on a weekly or biweekly schedule.[90] Liver function tests (serum bilirubin, AST and alkaline phosphatase levels) are not sensitive indicators of methotrexate-induced liver injury.[91] The only definite indicator of toxicity seems to be liver histology; a liver biopsy should be done yearly in patients receiving methotrexate for a long period. Histologic lesions include steatosis, ballooning degeneration of hepatocytes, portal fibrosis and cirrhosis. The fibrosis is rarely associated with hepatocellular failure, but micronodular or macronodular cirrhosis can result with continued methotrexate administration. A case of hepatoma in the setting of

methotrexate-induced fibrosis and cirrhosis has been reported in one patient.[92]

Peliosis Hepatis

Peliosis hepatis is an unusual lesion of the liver in which blood-filled lacunae of varying sizes are randomly distributed in the liver parenchyma. The drugs associated with these lesions are listed in Table 2. Peliosis hepatis is most often a pathologic finding but occasionally the cysts rupture with resulting hemoperitoneum.[81]

Hepatic Neoplasm From Antineoplastic Drugs

Hepatocarcinogenesis has been described with many drugs but the antineoplastic agents have only rarely been implicated (Table 2). Such tumors are unusual in patients undergoing chemotherapy, because prolonged administration of drugs affecting hormones is required to produce these tumors.

Antineoplastic Drug Dosage in Patients With Liver Disease

Although the occurrence of toxic effects on the liver from most antineoplastic drugs cannot be predicted from their pharmacokinetics, the presence of antecedent liver disease and the use of other drugs that affect liver enzymes may profoundly alter the metabolism of anticancer drugs. An overview of how major antineoplastic drugs are handled by the liver is shown in Table 3. Agents such as azathioprine, cyclophosphamide, dacarbazine (DTIC) and anthracycline antibiotics must be activated in the liver; serious underlying liver disease, abnormal liver blood flow and depressed activating enzymes can lead to inadequate peripheral drug concentrations. On the other hand, enhanced activating enzymes may lead to increased toxic effects. Liver enzymes also inactivate many antineoplastic drugs by a variety of metabolic pathways, and a few drugs (anthracyclines, *Vinca* alkaloids and podophyllotoxin derivatives) are excreted primarily through the biliary system. The diversity of liver disease seen in patients receiving chemotherapy makes it difficult to adjust drug dosage by following bilirubin and serum enzyme levels. Nonetheless, an empirically derived, useful table for dose modification was published recently.[117] Anthracycline antibiotics (especially doxorubicin and daunorubicin hydrochloride), *Vinca* alkaloids and podophyllotoxins should be reduced in dosage when there is mild to moderate liver dysfunction—that is, a serum bilirubin level of less than 5 mg per dl and a serum AST level of less than 180 U per ml—and probably omitted with more severe liver disease.[117] The metabolism of antimetabolites and alkylating agents is also abnormal in severe liver disease.

Pancreatitis Due to Antineoplastic Drugs

DR MCDONALD: Several antineoplastic drugs may cause pancreatitis (Table 4).[118] In most reported cases, pancreatitis has been self-limited, though deaths have been described with the use of L-asparaginase and prednisone.

Azathioprine

Patients receiving azathioprine and 6-mercaptopurine on a long-term basis for nonneoplastic diseases such as organ transplantation, Crohn's disease and renal dis-

TABLE 3.—*Role of the Liver in Metabolism of Antineoplastic Agents*

	Activation	*Inactivation*	*Biliary Excretion*	*Comments*
Antimetabolite				
Methotrexate[93,94]	0	+	+	Diglutamate metabolite retained in the liver
5-Fluorouracil[95]	0	+++	+	Activated in peripheral tissues
Cytarabine[95-97]	0	++	0	Activated in peripheral tissues
6-Mercaptopurine[98]	0	+++	0	.....
Azathioprine[99]	+++	+++	0	Converted to 6-mercaptopurine in liver
Alkylating Agents				
Cyclophosphamide[100,101]	+++	++	0	Complex sequence of activation; final step in tumor cells
Nitrosoureas[102-104]	0	++	+	Metabolism poorly understood
Busulfan[70]	0	++	0	.....
Dacarbazine[105,106]	+++	+++	0	.....
Natural Products				
L-Asparaginase[107]	0	++	0	May be retained in the liver
Anthracyclines[108,109]	++	+++	+++	.....
Bleomycin[110]	0	++	+	.....
Mitomycin C[111]	++	+++	0	.....
Mithramycin	0	?	?	Metabolism unknown
Dactinomycin[112]	0	0	++	.....
Other Agents				
Vinca alkaloids[113]	0	0	+++	.....
Epipodophyllotoxins[114]	0	+	+++	.....
Cisplatin[115]	0	?	0	Metabolism poorly understood
Procarbazine[116]	+++	+++	0	.....

0 = none, + = mild, ++ = moderate, +++ = pronounced

TABLE 4.—*Pancreatitis and Antineoplastic Agents*

Agents	*Latent Period*	*Comments*
Azathioprine and 6-mercaptopurine	3 wk	Symptoms resolve after drug therapy is stopped
L-Asparaginase	1-10 wk	Acute, severe pancreatitis in patients with leukemia
Estrogens	12 wk	Pancreatitis associated with hyperlipidemia; rarely severe
Prednisone	9 mo	Fatal pancreatitis occurs
Combination chemotherapy	Varies	Potential synergism between drugs

ease appear to be at highest risk for drug-induced pancreatitis.[119-126] The onset of pancreatitis in these patients was usually within three weeks of starting the drug regimen at 50 to 150 mg per day,[118] but in one case it occurred after a year of azathioprine therapy.[125] Symptoms subside upon withdrawal of the drug and reappear promptly after readministration.

L-Asparaginase

Pancreatitis related to L-asparaginase therapy has been recognized in patients with acute leukemia.[118,127,128] There is no clear relationship between drug dosage and pancreatitis and the latent period before clinical symptoms varies.[118,129] Serum amylase levels may be only minimally elevated, but pancreatitis can be rapidly fatal.[130]

Estrogens

Most patients with estrogen-related pancreatitis have been women taking estrogen by mouth for contraception, but pancreatitis has been reported to occur during therapy for prostate carcinoma.[118,131,132] Hyperlipidemia is common during an acute attack, and is usually indicative of an underlying disorder of lipid metabolism.[133,134] Higher estrogen doses may more likely cause hyperlipidemia and pancreatitis.[135]

Prednisone

There is circumstantial evidence that corticosteroids cause pancreatitis,[118] but some authors remain skeptical.[136] A relationship between corticosteroids and pancreatitis seems likely because of the high prevalence of pancreatitis in steroid-treated children, in autopsy series and in animals receiving steroids experimentally.[118,136-139] There is insufficient evidence to define the relationship of dose and latent period, but in most reported cases, the patients had been taking prednisone for many months.[118]

Combination Chemotherapy

There are several reports of pancreatitis in patients receiving multidrug chemotherapy.[118,122,136,140-142] In one patient pancreatitis developed twice after treatment with methotrexate, mitomycin-C, 5-fluorouracil, cyclophosphamide and vincristine.[141] Another patient had four episodes of pancreatitis after receiving cyclophosphamide, vincristine and doxorubicin.[142] Other case reports suggest synergism between cytarabine and L-asparaginase in causing pancreatitis.[140,143]

Nausea and Vomiting

DR TIRUMALI: The most common gastrointestinal symptoms associated with cancer chemotherapy are nausea and vomiting, which can lead to discontinuation of chemotherapy unless controlled.[144] These symptoms are probably due more to toxic effects on the central nervous system than to direct effects on the intestine. The physiology of vomiting and the mechanism of action of antiemetic agents have been reviewed recently.[145] The vomiting center is in the medullary reticular formation posterior to the fourth ventricle.[146] Adjacent to the vomiting center is the chemoreception trigger zone, which is a major source of afferent impulses to the emetic center. Most drugs and toxins mediate their emetic effect through stimulation of the chemoreception trigger zone, but few antineoplastic drugs have been studied with regard to how they cause vomiting. Mechlorethamine hydrochloride, a nitrogen mustard, exerts its emetic action by stimulation of the chemoreception trigger zone in dogs, but there are species variations that make inferences about humans difficult.[147]

Characteristics of Drug-Induced Vomiting

Table 5 lists antineoplastic drugs according to the severity of nausea and vomiting they produce. The prevalence and severity of nausea and vomiting increases with increasing dosages, especially with antimetabolite drugs. The time of onset of emesis after administration of the drug varies.[1] Vomiting is immediate with dacarbazine,[167] intermediate with mechlorethamine[168] and delayed and protracted with cyclophosphamide, doxorubicin and cisplatin.[169] When these drugs are used in combination, the emetic effect appears to be additive.

Antiemetic Drugs

Differences in the mechanism by which antineoplastic drugs produce vomiting may explain why no single antiemetic agent is uniformly effective in preventing emesis. Recent studies show that several classes of antiemetics are useful. Phenothiazines, butyrophenones and metoclopramide hydrochloride act as central dopamine antagonists.[170-173] Benzodiazepines and cannabinoids act on the cerebral cortex.[174] Both metoclopramide and domperidone have an additional effect on intestinal motility, but are effectively antiemetic only in very high doses.[175] Phenothiazines are ineffective in dealing with severe vomiting, but both canna-

binoids and high-dose metoclopramide are useful in these patients.[148,175] Haloperidol and droperidol may be effective with certain antineoplastic drugs.[176]

Many investigators have tested individual antiemetic agents in cases of vomiting produced by specific antineoplastic drugs (Table 5). Information about antiemetic effectiveness is not available for many regimens, however, particularly those that are combinations of antineoplastic drugs. Furthermore, these complex clinical studies have produced conflicting results regarding efficacy of antiemetic agents.

A reasonable, widely used approach is to give a combination of antiemetic agents before chemotherapy and to continue antiemetic therapy for 8 to 24 hours after the anticancer drugs are given. Sedation with haloperidol or droperidol combined with either high-

TABLE 5.—*Vomiting Caused by Antineoplastic Agents: Severity, Incidence and Antiemetic Therapy*

Agents	*Reported Incidence Percent*	*Antiemetic Therapy**		
		Effective	*Possibly Effective*	*Ineffective*
Severe Vomiting				
Cisplatin	100	High-dose metoclopramide hydrochloride[148] Droperidol[149]	Dexamethasone[150] Haloperidol[151] Nabilone[152] Methylprednisolone[153]	Low-dose metoclopramide[154] Prochlorperazine[148] THC[155,156] Benzquinamide hydrochloride[151]
Dacarbazine	100	THC[155] High-dose metoclopramide[157]	....	Prochlorperazine[158] .....
Mechlorethamine hydrochloride	100	THC[155]	Haloperidol[157]	.....
Nitrosoureas	70-90	THC[159] High-dose metoclopramide[160] Prochlorperazine[159]	....	....
Dactinomycin	...	†	.....	.....
Streptozocin	94	.....	Droperidol[161]	.....
Hexamethylmelamine	50-70	†	.....	.....
Daunorubicin hydrochloride	85	†	.....	.....
Drug combinations	100	THC[158] Nabilone[152] High-dose metoclopramide[162]	....	Prochlorperazine[152,158] ....
Moderately Severe Vomiting				
Cyclophosphamide	...	.....	Dexamethasone[150]	THC[163] Prochlorperazine[158]
Methotrexate	75	THC[164] High-dose metoclopramide[160]	....	Prochlorperazine[158] .....
Cytarabine	20-40	†	.....	.....
5-Fluorouracil	50-65	Prochlorperazine[165] THC[159]	Methylprednisolone[153]	Trimethobenzamide hydrochloride[166] .....
Mithramycin	89	†	.....	.....
Doxorubicin hydrochloride	60	High-dose metoclopramide[160]	Dexamethasone[150] Benzquinamide[151] Haloperidol[151]	..... THC[163] Prochlorperazine[158]
L-Asparaginase	50-60	†	.....	.....
Mild Vomiting				
Bleomycin	16	†	.....	.....
6-mercaptopurine	...	†	.....	.....
Busulfan	...	†	.....	.....
6-Thioguanine	...	†	.....	.....
Hydroxyurea	...	†	.....	.....
Procarbazine hydrochloride	...	†	.....	.....
Etoposide (VP-16-213)	...	†	.....	.....
Vinblastine	...	†	.....	.....
Melphalan	...	†	.....	.....
Tomoxifen	15	†	.....	.....

THC = tetrahydrocannabinol

*Based on published controlled studies.
†No published reports; the drugs above may be effective but are untested for a specific antineoplastic drug regimen.

dose metoclopramide or cannabinoids is one approach. However, a patient's prior experiences may be important, in that anticipatory vomiting occurs in about 25% of treated patients.[166] Behavioral therapy may reduce this frequency.[177] Antiemetic therapy is not risk free; central nervous system side effects are seen with all the antiemetic drugs.

Conclusions

DR MCDONALD: Intestinal symptoms after antineoplastic drug therapy are common but usually resolve without serious sequelae. More serious toxic effects on the gastrointestinal tract can be predicted by examining the drug dosage, its route of administration, concomitant therapy and underlying disease. Examples are intestinal mucosal necrosis after sequential chemotherapy regimens that include cytarabine, enhancement of drug toxicity by radiation therapy and the development of venocclusive disease of the liver in patients with hepatitis who are undergoing marrow transplantation. Other serious toxic reactions are sporadic and unpredictable.

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Medical Staff Conference

Oral Contraceptives and Benign Tumors of the Liver

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *It is our custom to ask the Chief Medical Residents at Moffitt Hospital (University of California, San Francisco [UCSF]) to present a Medical Staff Conference at the completion of their important position. A native North Carolinian, Dr Greg Fitz received his MD degree from Duke University School of Medicine before beginning house staff training at UCSF. Next year he will remain here as a member of the faculty, serving as Assistant Chief of Medicine at Moffitt Hospital. Because he has a special interest in gastroenterology, he has chosen the important topic of "Oral contraceptives and benign tumors of the liver." We want to express our appreciation to him for his important leadership role in our patient care and teaching program during this past year and during all of his years of training here.*

DR FITZ:† Ten years ago Janet Baum first suggested that there was an association between the use of oral contraceptives and the development of benign tumors of the liver.[1] Initially, this report was met with skepticism for these tumors were considered to be quite rare, but in the past decade more than 700 additional cases have been reported. These tumors have received a great deal of attention in the medical and popular press because of the alleged association with oral contraceptive use and because their benign histologic appearance often belies a threatening clinical course. Tumor hemorrhage or rupture is the initial manifestation of the disease in a significant number of previously healthy young women.

Because more than 50 million annual users of oral contraceptives may be at some risk of these tumors developing, it is important for clinicians to identify the patients at greatest risk and to be aware of the important clinical features of the illness. Unfortunately, this has been difficult because many authors have failed to distinguish between hepatic adenoma and focal nodular hyperplasia, the most common types of benign hepatic tumors. This has led to a great deal of confusion, for it appears that the clinical course, prognosis and relationship to oral contraceptives are different for the two types of tumors.[2] In view of this, I will review our experience with these lesions, paying particular attention to the clinical and epidemiologic distinctions between hepatic adenoma and focal nodular hyperplasia. I will begin this discussion by presenting a patient who was seen here recently.

Report of a Case

The patient, a 27-year-old black woman, was in excellent health until about six hours before admission when severe abdominal pain began abruptly. The pain was sharp, most severe in the periumbilical region and radiated to her back. She had had no previous gastrointestinal or gynecologic illness and she had started her normal period one day earlier. The patient had used a combination of norethindrone and mestranol (Ortho Novum 1/50) for the preceding six years but was taking no other medications.

On physical examination she appeared acutely ill and had severe abdominal pain. She was afebrile and while prone had a blood pressure of 100/60 mm of mercury and a pulse rate of 130. The blood pressure fell to 70/40 mm of mercury and the pulse rate increased to 140 when she sat up. There were no cutaneous stigmata of liver disease and her abdomen was distended and had decreased bowel sounds. There was diffuse tenderness, most severe in the mid-epigastrium and right upper quadrant, but there was no guarding or organomegaly. Cervical motion tenderness was present on pelvic examination. The admission laboratory studies

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
UCSF = University of California, San Francisco

showed a hemoglobin of 7.8 grams per dl, a hematocrit of 22% and a leukocyte count of 25,200 per μl. There was evidence of a metabolic acidosis and the serum creatinine level was 3.0 mg per dl. Chest x-ray film, kidney, ureter and bladder roentgenogram and electrocardiogram showed no abnormalities.

Initially the patient was felt to have a ruptured ectopic pregnancy. Her blood pressure became stable with administration of a normal saline solution, but she continued to have severe abdominal pain. Reexamination showed an enlarging pulsatile abdominal mass, and an emergency abdominal computed tomographic (CT) scan (Figure 1) showed a large nonhomogeneous mass in the left lobe of the liver with evidence of blood in the abdominal cavity. An emergency laparotomy was done and a ruptured mass in the left lobe of the liver was present, with extensive hemorrhage into the abdominal cavity. A partial hepatectomy was carried out but the procedure was complicated by severe bleeding requiring replacement of seven units of blood. The pathologic specimen showed a large (11 by 8 by 8 cm) hepatic adenoma (Figure 2). Ultimately, the patient recovered and is now doing well.

Historical Perspective

It is unlikely that the dramatic presentation of this patient would have been overlooked in the past, yet benign tumors of the liver were quite rare in the precontraceptive era. Edmondson found only two cases of hepatic adenoma in more than 50,000 autopsies done over a 36-year period in Los Angeles County General Hospital[3] and only four of these tumors were found over a 30-year period at Memorial Sloan-Kettering Cancer Center (New York).[4] Focal nodular hyperplasia was only slightly more common, with 14 cases detected in the same autopsy series by Edmondson.[3] Most of the latter tumors were detected as incidental autopsy findings in young women, but they occasionally occurred in children and in men.

In 1973 Janet Baum and her associates described the cases of seven women with hepatic adenoma in a five-year period.[1] This report attracted widespread attention because hepatic adenoma was still considered to be quite rare, and because all of the women were taking oral contraceptives. In addition, there was a frightening degree of serious hemorrhage in the patients. This initial report was followed by a flurry of other case reports linking oral contraceptive use to a wide variety of benign (and malignant) neoplasms of the liver. Unfortunately, it became apparent that many authors were not aware of the important pathologic distinctions between hepatic adenoma and focal nodular hyperplasia. This made it quite difficult to appreciate the distinct clinical and epidemiologic features of these tumors. Knowles and co-workers have drawn attention to one group of patients reported to have "benign hepatomas" in one journal, "focal nodular hyperplasia" in a second and "hepatic cell adenomas" in a third.[2] Other authors used terms such as focal cirrhosis, pseudotumor, solitary hyperplastic nodule or minimal deviation hepatoma to describe focal nodular hyperplasia or hepatic adenoma. It is understandable that most readers were confused.

Unfortunately, many of the major reviews of this topic have attempted to reclassify the cases reported in the literature without reexamining the pathologic specimens.[5,6] The validity of the original diagnosis cannot be assessed in these large series and it is likely that some inaccuracies occurred. Consequently one must view the results with a degree of skepticism. Because of the

Figure 1.—This abdominal computed tomographic scan shows a large low-density mass in the left lobe of the liver. The presence of hemorrhage in the mass and blood in the peritoneum suggests tumor rupture but the site of rupture is not seen.

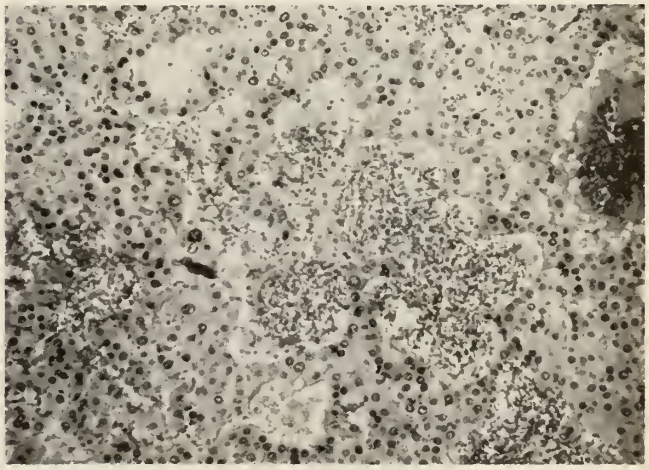

Figure 2.—The microscopic appearance of hepatic adenoma is dominated by sheets of normal-appearing hepatocytes without portal triads or bile ducts. Numerous thin-walled vessels are present, often accompanied by hemorrhage. (Hematoxylin and eosin stain, reduced from magnification ×200.)

confusion over the terminology of these tumors, I would like to review their pathologic characteristics before discussing more of the clinical and epidemiologic features.

Pathology

Despite the difficulties with nomenclature, the pathologic distinction between the two tumors is not difficult in most cases. The distinguishing features are outlined in Table 1. Focal nodular hyperplasia generally appears as a single nodule (78%) measuring less than 5 cm in diameter (84%).[7] The tumor arises from an otherwise normal liver, and on cut section there is a very characteristic central, stellate, fibrous core that radiates to the periphery of the lesion, dividing the tumor into a number of nodules. Histologically, the normal hepatic architecture (with central veins and portal triads) is completely replaced by normal-appearing hepatocytes in a lobulated pattern (Figure 3). There is prominent, haphazard bile duct proliferation in the fibrous septae and chronic inflammatory cells are frequently seen. Classically, there is no capsule surrounding these tumors.[2] Areas of hemorrhage, infarction and necrosis are uncommon in this tumor. In some reports, there is an interesting and unexplained association between focal nodular hyperplasia and cavernous hemangioma seen in 2% to 20% of the patients who have the former.[7] Gallbladder abnormalities are seen in many of these patients but it may be that biliary tract symptoms draw attention to tumors that would otherwise go unnoted.[7]

The cause of focal nodular hyperplasia is unknown. Because the lesion contains many different cellular elements, it may not be a primary neoplasm at all. Whelan and colleagues have suggested that focal hepatic injury from congenital abnormalities in the blood supply or biliary drainage may cause injury, healing and regeneration that result in tumor formation.[8] There is no convincing evidence that this lesion undergoes malignant change or is associated with hepatocellular carcinoma.[2,7]

Hepatic adenoma is generally easily distinguished from focal nodular hyperplasia by gross and microscopic inspection. It usually appears as a single (71%) large (36% larger than 10 cm) fleshy tumor without any internal structure.[7] The surrounding liver is normal in appearance but intratumor hemorrhage or infarction occurs frequently. The microscopic appearance of hepatic adenoma is dominated by sheets or cords of hepatocytes that often appear pale or vacuolated due to glycogen storage. The absence of bile ducts is noteworthy. This type of lesion tends to be a much more vascular lesion than focal nodular hyperplasia, with many thin-walled dilated venous structures resembling central veins and giving a peliosis-like appearance

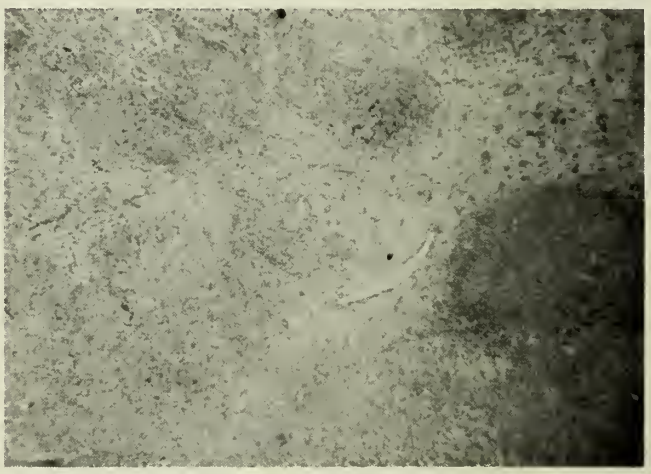

Figure 3.—Focal nodular hyperplasia contains a central, stellate, fibrous core. Proliferating bile ducts and inflammatory cells are often seen in the fibrous areas. The hepatocytes are arranged in lobules by the septae and are normal in appearance. (Hematoxylin and eosin stain, reduced from magnification ×90.)

TABLE 1.—*Comparison of the Clinical and Pathologic Features of Hepatic Adenoma and Focal Nodular Hyperplasia*

Features	*Hepatic Adenoma*	*Focal Nodular Hyperplasia*
Clinical		
Age	20 to 40	All ages
Sex	~95% female	~60% female
Oral contraceptive use	Almost always	Common
Presentation		
Shock, tumor rupture	~35%	Less than 1%
Hemorrhage	~25%	Less than 1%
Abdominal pain	Common	Common
Palpable mass	Common	Common
Incidental	Uncommon (~5%)	Up to 80%
Pathological		
Appearance	Large, fleshy, homogeneous	Central stellate scar
Hemorrhage	Common	Rare
Fibrous core	Absent	Present
Capsule	Present	Absent
Hepatocytes	Normal	Normal
Bile ductules	Absent	Proliferating
Kupffer's cells	Absent	Present
Vasculature	Large, thin-walled venous spaces	Intimal and medial changes

(Figure 2).[5] In addition, hemorrhage, necrosis and infarction are much more common in hepatic adenoma than in focal nodular hyperplasia.[5,9] There is still some confusion about the malignant potential but the risk, if present, is very low.[2] These features make it almost certain that hepatic adenoma results from the neoplastic transformation of a normal hepatocyte.

There are several reasons to suspect that the major effect of oral contraceptive use may be on the vasculature of these tumors. Klatskin reported that oral contraceptive-associated hepatic adenoma or focal nodular hyperplasia was larger, more vascular and more prone to hemorrhage than either of these lesions when not associated with oral contraceptives.[5] It is noteworthy that the pathologic specimens were not reviewed in this report so the accuracy of the original diagnosis is uncertain. This does not negate the association between hemorrhage and oral contraceptive use. In a more careful study of 94 cases, Nime and associates found that focal nodular hyperplastic lesions occurring in pill users were larger and had more vascular alterations, fibrosis and peliosis than did those occurring in patients who did not take oral contraceptives.[9] Hemorrhage, necrosis and peliosis were much more common findings in hepatic adenoma than in focal nodular hyperplasia, and all 27 cases of hepatic adenoma were found in patients taking oral contraceptives.

Clinical Experience at UCSF

During the past 15 years there have been 17 patients with a pathologic diagnosis of benign hepatic tumor seen at this institution. Seven patients had hepatic adenoma, six had focal nodular hyperplasia and four are not included in this series because their charts were not available for review (one had hepatic adenoma, one had focal nodular hyperplasia and in two the diagnosis was unknown). The clinical features of these patients are shown in Table 2. It is noteworthy that six of the seven cases of hepatic adenoma were detected after 1977, but the six cases of focal nodular hyperplasia were distributed evenly over the review period.

In this small series of patients there are several striking differences between the two types of lesions. All of the patients with hepatic adenoma were women of child-bearing age, all had a history of prolonged oral contraceptive use and four of them presented with acute tumor hemorrhage or rupture as the initial manifestation of the disease. By contrast, focal nodular hyperplasia was seen in one man, one child and one postmenopausal woman; there was no significant history of oral contraceptive use and none of the patients had life-threatening hemorrhage. These findings strongly suggest an association between taking oral contraceptive drugs and the development of hepatic adenoma, but no association with focal nodular hyperplasia is present in this series. These findings are at odds with many of the earlier reports on this subject, and support the contention of Knowles and co-workers that focal nodular hyperplasia is associated with oral contraceptive drug use on a coincidental basis only.[2]

Incidence

Central registries for benign liver tumors are recent developments so it is difficult to estimate the actual change in the incidence of these lesions. Despite this, it is clear that benign liver tumors are increasing in frequency, and it appears that most of this increase is accounted for by an increase in the incidence of hepatic adenoma.[2] The recent increase in cases of this disorder seen at our institution supports this opinion. Perhaps the best estimate of the relative frequency of these tumors comes from the American College of Surgeon's Commission on Cancer.[6] In this retrospective study of more than 400 hospitals, 226 benign hepatic tumors were detected. Of these, 212 (94%) occurred in women, including 96 who had hepatic adenoma, 58 who had focal nodular hyperplasia and 33 with hamartoma. The pathologic specimens were not reviewed to confirm the original diagnosis but it is still significant that hepatic adenoma was diagnosed almost twice as often as focal nodular hyperplasia. Other authors have also noted the preponderance of cases of hepatic

TABLE 2.—*Clinical Features of Hepatic Adenoma and Focal Nodular Hyperplasia in Cases at University of California, San Francisco*

Age, Sex	*Duration of Oral Contraceptive Use*	*Association With Menstruation*	*Clinical Presentation*
Hepatic Adenoma			
27 ♀	.... 6 yr	Yes	Shock, tumor rupture
24 ♀	.... 7 yr	Yes	Shock, tumor rupture
36 ♀	....15 yr	Unknown	Hemorrhage, abdominal pain
29 ♀	.... 6 yr	Yes	Hemorrhage, abdominal pain
36 ♀	....15 yr	No	Fever and abdominal pain for 14 mo
49 ♀	.... Unknown	Unknown	Abdominal pain for 3 mo, palpable mass
23 ♀	.... 5 yr	No	Incidental
Focal Nodular Hyperplasia			
54 ♀	.... None	No	Abdominal pain for 1 yr
40 ♀	.... Unknown	No	Abdominal pain for 14 mo
49 ♂	.... None	...	Abdominal fullness for 5 mo
10 ♀	.... None	No	Abdominal pain, hepatomegaly
27 ♀	.... 4 mo	No	Incidental
22 ♀	.... 3 mo	No	Incidental

adenoma in recent years.[2,10] This is a clear reversal from Edmondson's series in the precontraceptive era wherein cases of focal nodular hyperplasia outnumbered those of hepatic adenoma by 14 to 2.[3] This suggests that the increase in the occurrence of hepatic adenoma is responsible for most of the recent increase in benign tumors of the liver.

These findings do not eliminate the possibility that cases of focal nodular hyperplasia have also increased in frequency but to a lesser degree. Any increase in the number of these tumors could be due to an actual increase in the incidence of the disease, a change in the symptoms that brings these patients to the attention of doctors more frequently or improved detection through the use of advanced imaging techniques. All three factors probably play a role in hepatic adenoma, but there is no clear evidence that the incidence of focal nodular hyperplasia has changed greatly since the precontraceptive era.

Age and Sex

The age and the sex of the patients seen at our institution are very representative of the patients reported in the literature. Hepatic adenoma was found exclusively in women of reproductive age, with an average age of 32 years (range, 23 to 49). Focal nodular hyperplasia was observed in one child, one man, one postmenopausal woman and three women of reproductive age. The mean age of 34 years was similar but the range was much greater in the patients who had focal nodular hyperplasia (range, 10 to 54 years).

Both of these tumors are more common in young women, but in recent years hepatic adenoma has been seen almost exclusively in this group. Ishak and Rabin reported 75 cases of hepatic adenoma seen at the Armed Forces Institute of Pathology and all occurred in women between the ages of 17 and 61 years, with a peak incidence in the third and fourth decades.[7] In a second large series, 96 of 101 patients with this tumor were women, and the peak incidence was between the ages of 21 years and 35 years.[6] It is possible that the five men with hepatic adenoma did not actually have this disorder because this was a retrospective review of other pathologists' data. Up to a third of the patients with focal nodular hyperplasia are men or children.[7] It does not appear that this has changed in the contraceptive era, and this is an important clue concerning the pathophysiology of these lesions.

Relationship to the Use of Oral Contraceptives

The most striking difference between the cases of hepatic adenoma and those of focal nodular hyperplasia in our series is the prolonged use of oral contraceptives in patients with hepatic adenoma. Six of the seven patients who had this tumor took oral contraceptives for an average of nine years (range, 5 to 15 years) before the recognition of the tumor; this drug history is unknown in the other patient. None of the patients with focal nodular hyperplasia had a history of significant oral contraceptive use (one patient took them for four months, eight years before the diagnosis, and a second patient took them for three months, two years before the diagnosis). This dramatic difference in oral contraceptive drug use is not seen in most of the reports in the literature. Despite some reports to the contrary,[11] there is no clear evidence that supports a causal link between the use of oral contraceptives and the development of focal nodular hyperplasia. Such evidence does exist for hepatic adenoma. Oral contraceptive use is quite widespread in our society and a history of such use would be expected by coincidence alone in many patients who have benign liver tumors. In view of this it is important to critically examine the literature linking its use to the development of hepatic adenoma and focal nodular hyperplasia.

As a result of the common use of oral contraceptives by young women, most women who have either of these lesions do have some history of taking these drugs. In the American College of Surgeons' review, 74% of women with hepatic adenoma as well as 74% of the women with focal nodular hyperplasia had taken oral contraceptives.[6] However, the duration of exposure was much shorter for focal nodular hyperplasia (less than two years for 48% of the patients) than for hepatic adenoma, implying that there might be a difference between the two.

The most compelling evidence for the important role of oral contraceptive use in the pathogenesis of hepatic adenoma comes from two retrospective case-control studies. Edmondson and associates compared 34 women who had hepatic adenoma with an equal number of well-matched controls.[12] Most of the cases (29 of 34) and controls (24 of 34) were found to have a history of oral contraceptive drug use, but the average duration of use was more than 6½ years for the cases, compared with only three years in the controls. The risk of hepatic adenoma developing rose dramatically with increasing duration of oral contraceptive use. In women who had used oral contraceptives for more than six years, hepatic adenoma was 25 times more likely to develop than in nonusers. Similar but more dramatic results were obtained in a case-control study carried out by the Centers for Disease Control and the Armed Forces Institute of Pathology.[13] In that study, 79 patients with documented hepatic adenoma were compared with 220 age- and neighborhood-matched controls. The most significant difference between the cases and the controls was the prolonged use of oral contraceptives in the patients with adenoma: 52% of these patients had used oral contraceptives for more than five years but only 12% of the controls had done so for a similar period. Once again, as the duration of therapy increased the risk of hepatic adenoma developing increased. The use of the pill for three, five or more than seven years resulted in a relative risk for the lesion developing of 9, 116 and 503, respectively. In each of these independent studies, findings strongly support a causal association between the prolonged use of oral contraceptives and the development of the tumor.

Oral contraceptives contain either mestranol or ethinyl estradiol as the synthetic estrogen. Early reports suggested that mestranol use was more common than ethinyl estradiol use in patients who had hepatic adenoma and therefore mestranol was the more likely carcinogen.[5] This observation has not been supported in later studies.[13] Possibly because mestranol has been used for a longer period of time, a history of its use is more likely to occur in the long-term users of oral contraceptives.[13] In our own series, there was insufficient information about the type of contraceptive drug used, so no comment can be made about this. At present, mestranol and ethinyl estradiol should be considered as equal offenders.

Unfortunately there are no studies that carefully examine the epidemiologic link between oral contraceptive use and the development of focal nodular hyperplasia. Although there is some evidence that the use of the pill may increase the size of or symptoms from this tumor, further studies are needed before any causal association can be detected. The association in the literature seems to be no more than would be expected from coincidence alone.[2]

Clinical Presentation

The second major difference between hepatic adenoma and focal nodular hyperplasia is the frequency of serious hemorrhage complications. Four of our seven patients who had hepatic adenoma presented with life-threatening hemorrhage as the initial manifestation of the tumor. Two of these had circulatory collapse as a result of intraperitoneal rupture of the tumor, and two had the acute onset of right upper quadrant pain from hemorrhage within the tumor. By contrast, none of our patients with focal nodular hyperplasia had significant hemorrhage. This major difference in clinical presentation is common to all reports of both types of hepatic tumors.

Most patients who have hepatic adenoma are symptomatic at the time of diagnosis. Klatskin reported that 41% of his 79 patients presented with tumor rupture, shock and hemoperitoneum and an additional 27% had acute abdominal pain from tumor hemorrhage.[5] Sorensen and Baden found that 44% of 69 patients with hepatic adenoma had symptoms from tumor rupture or hemorrhage.[14] A palpable mass is present in most patients who present with acute hemorrhage.

The other presenting symptoms of patients who have hepatic adenoma are a palpable mass (22%[5] to 43%[12]) or intermittent abdominal pain (1%[5] to 28%[12]); occasionally the tumors are detected as incidental findings during evaluation for other problems (less than 5%[12]). One of our patients had a 14-month history of intermittent right upper quadrant pain and fever that resolved after resection of the tumor.

In the patients who present with acute tumor hemorrhage or rupture, the pain is abrupt in onset and is most severe in the mid-epigastrium and right upper quadrant. The low hematocrit and abdominal distension are sometimes indistinguishable from a ruptured ectopic pregnancy or a ruptured spleen. Blood is present in the abdominal cavity and is recovered by culdocentesis or paracentesis. It is important to realize that a physical examination generally elicits hepatomegaly or a palpable abdominal mass in the majority of the acutely ill patients.[2] The patients who present with vague abdominal pain are generally misdiagnosed as having biliary tract disease, ulcer disease or menstrual disorders unless an abdominal mass is noted or the index of suspicion is high.

There seems to be an interesting association between menstruation and acute hemorrhage of these tumors. This has been noted by several authors[12,13] and three of the four women in our series who presented with acute tumor hemorrhage were having their menstrual period. This observation underscores the importance of hormonal influence on hepatic adenoma. Although the mechanism of this influence is unknown, it has been suggested that this represents a hormonally mediated constriction of the large arteries that supply these tumors.[12] This is analogous to the spasm of the spiral arterioles of the endometrium that results in menstrual bleeding.

In contrast to the threatening clinical course of hepatic adenoma, patients who have focal nodular hyperplasia generally have no symptoms and the prognosis is excellent. Ishak and Rabin reported that only 20% of 130 patients with this lesion had any symptoms referable to the tumor and 80% of the tumors were incidental findings[7]; 45% of these were found during laparotomy for other reasons and 35% of the tumors were incidental findings at autopsy. In a recent review of the literature, 35% of 141 patients who had focal nodular hyperplasia presented with an abdominal mass or nonspecific abdominal pain, nausea or altered bowel habits.[14] Knowles and Wolff reviewed 20 cases and in every case the tumor was an incidental finding.[15] Serious hemorrhage has been reported as a complication of this condition but it is quite rare. Knowles and co-workers could find only two well-documented cases in the literature.[2] This is interesting in view of two major reviews that found hemorrhage in 3.5%[6] to 21%[5] of these patients. The latter studies were based on cases reported in the literature and there was no formal review of the histologic findings. The higher incidence of bleeding in these reviews could be the result of inaccurate classification of the tumors.

Laboratory Diagnosis

When a benign tumor of the liver is suspected on the basis of history or physical examination, routine laboratory studies have been of little help in establishing a diagnosis. Hepatocellular carcinoma tends to occur in patients who have preexisting liver disease, but benign tumors of the liver generally arise from normal tissue. Consequently routine liver function tests generally show normal results even with very large tumors. Modest elevations of serum bilirubin, alkaline phosphatase and aminotransferase levels may occur as a result of tissue necrosis from tumor hemorrhage, but

the pattern of elevation is entirely nonspecific.[5] Careful attention to the clinical history and physical examination is much more productive than routine laboratory testing in the early detection of these tumors.

The radiographic distinction between the two types of tumors has been hampered by the lack of accurate histopathologic correlation. Ideally, a radiologist should be able to detect the tumor and then distinguish between the two because of the good prognosis of focal nodular hyperplasia. Unfortunately, the tumors can be differentiated in only half of the cases.[2] As a result, most of these patients require surgical intervention for definitive diagnosis and treatment.

There are no well-documented reports about the efficacy of ultrasonography in benign liver tumors. In our series, three patients—two with hepatic adenoma, one with focal nodular hyperplasia—had an ultrasound study and all of the tumors were detected. The study was very helpful in distinguishing solid from cystic lesions but could not differentiate between the two types of benign hepatic tumors.

There has been much more experience with technetium Tc 99m sulfur colloid liver scans. Normally this radioligand is taken up by Kupffer's cells and is then detected on a scintillation camera. Most mass lesions of the liver do not contain Kupffer's cells and are seen as "cold" spots on a scan. The sensitivity of this test is only 70% to 80% for both types of lesions[5,16,17] and this is a disappointing yield for such large tumors. Focal nodular hyperplasia may be particularly hard to detect for it is composed of all of the normally functional parenchymal cells including Kupffer's cells. In one review of 16 cases, nine of the tumors appeared as cold spots, five of the scans showed no abnormalities and two scans actually showed an increase in the uptake of the radiocolloid.[17] The same report documents hepatic adenoma up to 20 cm in size with normal findings on ^{99m}Tc sulfur scans. These studies are helpful in detecting these tumors, but the findings are nonspecific and the false-negative rate is high.

The most valuable study in the assessment of hepatic tumors is hepatic arteriography. The tumors generally appear as hypervascular masses with a dense capillary blush.[5] Most authors have not been able to distinguish hepatic adenoma from focal nodular hyperplasia but Knowles and associates were able to do so in more than half of their patients.[2] The most helpful finding was visible septation of the tumor mass during the capillary phase, suggesting focal nodular hyperplasia. This septation was not seen in any patient with hepatic adenoma but hypovascular areas from tumor hemorrhage or necrosis were present in hepatic adenoma. In the same study the authors report that combined angiography and radionuclide scan accurately differentiated the tumors in 17 of 27 cases. The clinical and arteriographic features of hepatocellular carcinoma usually distinguish it from these lesions.

CT scanning promises to be of great benefit in the detection of these tumors. In our series, ten patients—five with hepatic adenoma and five with focal nodular hyperplasia—had an abdominal CT scan and the tumor was detected in all cases. The tumor generally appeared as a low-density mass lesion, and areas of hemorrhage were common in hepatic adenoma (Figure 1). There is not enough experience with this technique to accurately assess the sensitivity and specificity or to distinguish the two types of tumors on a reliable basis.

With the limitations of these diagnostic studies in mind, the most difficult question is to decide which patients need further investigation. There is no question that detection of hepatic adenoma before rupture occurs would improve the outcome.[13] Millions of women use oral contraceptive drugs on a regular basis. Most of them have abdominal pain on occasion, yet benign tumors of the liver are still quite uncommon. Clearly the index of suspicion should go up in patients who have taken oral contraceptives for three years or more or when there is any suggestion of hepatomegaly or a mass on physical examination. Routine liver function tests would not be expected to be helpful but are generally done because of the concern about biliary tract disease. Despite the limitations of radionuclide scans, I favor the ^{99m}Tc sulfur colloid liver scan as the next step in evaluating stable patients, recognizing that one in five of the lesions may be missed. Further studies (CT or arteriography) may be needed if the clinical suspicion is high.

Diagnosis and Therapy

The use of birth control pills should be stopped in all patients who may have hepatic tumors because there are several well-documented reports of tumor regression after withdrawal of the drug. The great majority of patients will require biopsy or excision of the lesion for therapy or definitive diagnosis. Percutaneous needle biopsy has been successful in a number of patients, but hepatic adenoma is a very vascular tumor and needle biopsy may be complicated by tumor hemorrhage.[5] Consequently, an open surgical procedure is preferred in most cases.[2]

The overall mortality of hepatic adenoma is about 8%,[5] and nearly all of the deaths are related to tumor rupture or hemorrhage. Consequently, any patient who has this lesion with or without symptoms should have a surgical resection because of the frequent complications from the tumor. A surgical procedure is well tolerated in this group because the patients are generally healthy and are without other hepatic dysfunction.

In patients who are at increased risk from an operation and who have minimal symptoms, it is reasonable to withdraw the drug and follow them closely for a period. There are at least nine well-documented reports (and more anecdotal reports) of regression of these tumors once the drug is withdrawn.[5,18] Unfortunately, at least as many tumors fail to regress or even enlarge after withdrawal of the oral contraceptive.[5,19] Obviously close clinical and radiographic follow-up is essential, and any evidence of hemorrhage, enlargement or doubt about the diagnosis should dictate operative management. Even after resection of these tumors, oral

contraceptive use is contraindicated because the recurrence rate is higher than 10% in patients who continue to use these agents.[5,13] In the absence of continued oral contraceptive use, the prognosis after resection of hepatic adenoma is excellent.

In patients who have focal nodular hyperplasia, the only clear indications for surgical resection are the presence of symptoms or uncertainty about the diagnosis. When asymptomatic, the prognosis is excellent.[2,15] It has been suggested that the principal complication of this benign liver tumor is the morbidity or mortality of a surgical procedure done because of uncertainty about the diagnosis.[2] All of the patients in our series had tumor excision because the diagnosis could not be established with certainty before operation. Surgical resection of the tumor is curative and the prognosis after recovery is excellent.[2,12]

Mechanism of Action

It should be clear from the preceding discussion that hormonal factors are very important in the pathogenesis and clinical presentation of hepatic adenoma. The great majority of the tumors occur in women of reproductive age, hemorrhage frequently occurs in association with menstruation, regression of these tumors may follow cessation of oral contraceptive therapy and tumor recurrence has been noted when the use of the drug is continued. Unfortunately, the mechanism of this influence is unknown. It is not without precedent to speculate that estrogens might promote tumor formation in the liver. The liver is a target organ for estrogen, and estrogens have been implicated in tumor formation in other hormonally sensitive organs such as the uterus, vagina and breast. Although oral contraceptives contain synthetic estrogens and progesterones, most authorities feel that the weight of the evidence indicts synthetic estrogens as the culprit but progestational agents have not been rigorously excluded.

Birth control pills contain one of two synthetic estrogens, mestranol or ethinyl estradiol. These are both derived from C_{17}-substituted androgens and differ only by the methylation of the hydroxyl group at C_3.[12] Consequently, mestranol is first metabolized by the liver to yield ethinyl estradiol. Substitution in the 17α position is a very effective metabolic hindrance and serves to decrease bile flow and sulfobromophthalein sodium clearance and to increase cell membrane permeability.[20] In short, the synthetic estrogens used in oral contraceptives clearly perturb normal hepatocyte function.

Although there is considerable disagreement in the literature, most authorities support the concept that synthetic estrogens serve as tumor promoters.[21] Tumor initiation occurs when a normal cell is converted to a neoplastic one—such as by irradiation—and tumor promotion occurs when this abnormal cell is stimulated to tumor formation. When rats are exposed to synthetic estrogens alone there is no apparent risk of hepatic tumor formation. When rats treated with the known carcinogen *N*-nitrosomorpholine are exposed to estrogen, the number of hepatic neoplasms triples above that seen after exposure to the carcinogen only.[22] These findings imply that synthetic estrogens do not cause tumors directly but can enhance the growth of neoplastic cells. Data such as these cannot be applied directly to humans but they may be relevant to the changing epidemiology of hepatic adenoma.

Conclusion

In recent years the prevalence of benign tumors of the liver has increased to the point that they must now be considered in the differential diagnosis of a variety of symptoms in women at risk. It is important to distinguish hepatic adenoma from focal nodular hyperplasia for the former may be complicated by severe hemorrhage and is clearly linked to prolonged use of oral contraception. Focal nodular hyperplasia has an excellent prognosis and, despite some reports to the contrary, there is no clear evidence that synthetic hormone use has resulted in a change in the frequency of this tumor. It is estimated that the annual incidence of hepatic adenoma is now 3.4 cases per 100,000 oral contraceptive users and at this rate about 320 new cases are expected each year.[13] There is no question that careful scrutiny of the group at risk offers the best chance of preventing serious morbidity from hepatic adenoma.

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Epitomes

Important Advances in Clinical Medicine

Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in ophthalmology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Steroid-Induced Glaucoma

STEROID-INDUCED increase of intraocular pressure has been described for more than 30 years; however, it remains a cause of visual loss and iatrogenic glaucoma. Unfortunately, steroid drops are often prescribed for relatively minor conditions such as blepharitis or eye irritations, conditions for which steroids are often unnecessary. Steroids decrease outflow facility, resulting in a condition simulating primary open-angle glaucoma. If prolonged intraocular pressure elevation occurs, damage results to the optic nerve with irreversible loss of visual field.

Both endogenous and exogenous steroids may induce pressure elevations in susceptible persons. Topical, periocular and systemic steroid medications are involved in the vast majority of cases. Even steroid preparations applied to the skin away from the eye may induce elevations of intraocular pressure. Susceptibility to topical steroids has been tested extensively. From these studies a substantial percentage (33%) of the population were found to be at risk, particularly patients with preexisting open-angle glaucoma and their first-degree relatives. In addition, persons with myopia and those with diabetes mellitus are also at increased risk. The degree of pressure elevation depends on individual susceptibility and the concentration, duration and frequency of the dose. Increased intraocular pressure may occur as early as one to two weeks or as late as months to years after initiation of therapy.

The clinical spectrum of corticosteroid-induced glaucoma varies with a patient's age. In infants often treated with topical steroids as part of an antibiotic-steroid combination, the disease simulates congenital glaucoma with an enlarged eye and corneal edema. In older children and adults, the disorder resembles primary open-angle glaucoma, and is often asymptomatic.

The most effective treatment of steroid-induced glaucoma is discontinuation of the corticosteroid. Within a few days to weeks, a prompt reduction of intraocular pressure occurs. Occasionally the increased pressure persists. If this occurs or if the steroid therapy must be continued, standard antiglaucoma medications may lower the pressure. If unsuccessful, laser or intraocular surgical treatment may be necessary for glaucoma management.

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Macular Degeneration

MACULAR DEGENERATION is the leading cause of new blindness in the United States and accounts for 14% of cases of new blindness in persons older than age 65 years. Age-related macular degeneration covers a wide spectrum of clinical disease and visual dysfunction. The prevalence of this disease in the older-than-50-years age group is very high but only a small percentage of persons have severe visual loss.

Some degree of visual loss is associated with a nonexudative degeneration that is characterized by drusen (yellow deposits on Bruch's membrane) and epithelial derangement of the retinal pigment. The more severe form of degeneration often leading to legal blindness is manifested by hemorrhage and exudation originating from choroidal neovascularization in the macula. This frequently leads to a disciform scar destroying the sen-

sory retina. The pathologic process includes degeneration and breaks in Bruch's membrane (a barrier layer separating the retina and choroid), which allows choroidal vessels to invade the space beneath the retina (choroidal neovascularization) and leak fluid or blood.

Until a recent study by the Macular Photocoagulation Study Group, supported by grants from the National Eye Institute, the treatment of exudative macular degeneration by obliteration of choroidal neovascularization with argon laser photocoagulation had not been proved. A multicenter controlled clinical trial was undertaken in 1980 to answer the question "Is argon laser photocoagulation useful in preventing severe visual loss in eyes with evidence of macular degeneration and a choroidal neovascular membrane outside the fovea?" As few as 1 in 20 patients screened met the eligibility criteria. Of those patients selected, however, by 18 months after entry in the study, 60% of the patients whose eyes were untreated had lost six or more lines of vision compared with only 25% of those whose eyes had been treated. Twice as many patients whose eyes were treated had a visual acuity better than 20/40 at the most recent visit. Persistence of the treatment benefit remains to be determined.

Patients at greater risk, such as those who have lost central vision from exudative macular degeneration in one eye, should be examined periodically. Because persons are in the treatable stage for only a short time after onset of symptoms, it is important for both physicians and patients to be alert for symptoms of distortion, scotoma or blurred vision that may indicate the presence of choroidal neovascularization. Further investigation is being done in hopes of finding other laser wavelengths that may increase the success rate in this vision-threatening disease.

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Severe Systemic Effects From Topically Applied β-Adrenergic Blocking Agents

RECENTLY, β-adrenergic blockers (timolol maleate) have become commercially available for the medical treatment of open-angle glaucoma. These topically applied drugs lower intraocular pressure by decreasing the rate of aqueous humor formation. They are usually effective both alone and in combination with other ocular hypotensive agents in lowering intraocular pressure in an attempt to prevent the optic nerve damage and visual field loss that can ultimately lead to blindness.

Topically applied timolol can be associated with all the side effects characteristic of β-blocking adrenergic drugs. Severe systemic depression, bronchospasm and even death have been described in some patients using this medication. Topically applied β-blockers are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, and in patients who have had cardiac failure. Furthermore, special care must be taken to instruct patients in the proper technique of eye-drop installation to minimize systemic absorption from the vascular nasal mucosa.

After installation of a drop, the patient should apply gentle pressure along the side of the nose, over the lacrimal sac. This maneuver enhances intraocular drug penetration and minimizes nasal mucosal absorption.

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Endothelial Cell Counts

ENDOTHELIAL CELL COUNTING is one method used to determine the health, longevity and surgical vulnerability of a human cornea. A cornea maintains its clarity if there are enough endothelial cells covering its back surface to continuously pump fluid from it. This one-cell-thick layer of tissue does not replace itself by mitosis. Damaged cells are replaced by neighboring cells stretching to cover the denuded area. The more cells there are the more "reserve" the cornea has to withstand trauma and cell loss. Therefore, it is of clinical importance to know the cell population or cell density of a given cornea.

The technique of endothelial cell counting was first popularized by Bourne and Kaufman in 1975. The procedure is done using a specifically designed endothelial specular microscope that allows high-magnification photography of the actual endothelial cells in vivo. The microscope is calibrated with an internal grid so that the cells in a defined area can be counted much like blood cell counts. The count is reported as cells per sq mm. The microscope is expensive, the technique requires skill and the counting is time-consuming.

The cell density of the human cornea is higher at birth than in old age, the loss of cells being due to attrition. Hoffer and Kraff found that mean cell density in the age range of 40 to 90 years old is 2,400 cells per sq mm and that age was not useful as a predictor of cell density. In one study, in eyes with cell counts of less than 350 cells per sq mm, a cloudy, painful cornea (bullous keratopathy) developed within two years, requiring corneal transplantation. There are many causes of cell loss but surgical trauma is the most common and the most likely in elderly persons. Because patients whose eyes have low counts are at greater jeopardy, it is wise to know the cell density of an eye before considering an intraocular anterior segment operation, such as a cataract extraction with lens implantation. A small percentage of persons have corneas with very low cell density for unexplained reasons and this must be known before a surgical procedure. Because patients who have had a previous eye operation most likely have lower cell density, it is extremely important to do endothelial cell counts on those who are

to have a secondary procedure such as a secondary lens implantation.

There are less accurate methods of "estimating" cell density using an ophthalmic slit-lamp microscope. This technique uses a simple estimating comparator and does not require the counting of cells in photographs.

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Corneal Transplantation

CORNEAL TRANSPLANTATION is an accepted and highly successful therapeutic tool in ophthalmologic surgical procedures. Advanced microsurgical techniques, increased understanding of transplant immunology and the availability of topical corticosteroids have afforded the corneal allograft a degree of success unmatched by transplantation attempts with other tissues. Allograft rejection remains, nonetheless, a problem. Graft rejection attempts occur in about 20% of patients, though the percentage of grafts opacified from immune rejection is considerably smaller.

The mainstay of preventive immunosuppressive therapy has been topical and systemic corticosteroids. The success of these agents depends to a great extent on the vascularity of the recipient bed. The prognosis for graft survival remains only poor to fair in cases in which the host cornea is heavily vascularized.

Despite the success of topical corticosteroids in controlling the graft reaction, they can be associated with potential side effects including steroid-induced glaucoma, cataract, bacterial superinfection and herpetic recurrences. Therefore, alternative methods of immunosuppression have been evaluated. Most recently cyclosporine, a potent T-cell inhibitor that has revolutionized vital organ transplantation when administered either topically or as a retrobulbar injection in the laboratory, has shown promise as a useful immunosuppressive agent in clinical corneal grafting.

Human leukocyte antigen typing has been neither necessary nor practical in corneal transplantation primarily because of the avascularity of the cornea. Recent studies have indicated, however, that in selected heavily vascularized (high-risk) patients, human leukocyte antigen crossmatching or negative crossmatching of circulating lymphocytotoxic antibodies may improve the prognosis for graft survival.

In most cases, however, the prognosis for an optically clear graft is very good. Recipients can be educated in the cardinal danger signs of graft rejection (pain, redness, decreased vision) and, with early recognition and prompt and aggressive local immunosuppression, a clear corneal graft can be maintained.

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Intraocular Lenses for Correction of Aphakia

BEFORE intraocular lenses, the vision of the average postcataract operation patient was corrected with either thick, heavy spectacles or contact lenses. Although most patients can eventually adjust to cataract glasses, problems with depth perception, restriction of peripheral vision and image magnification often remain. Contact lenses eliminate most of these optical problems but require some degree of manual dexterity and a healthy cornea. Despite improvements such as daily-wear soft and extended-wear contact lenses, many patients still fail to achieve satisfactory comfort or visual correction. Intraocular lenses return an eye to an optical condition similar to that preceding the development of the cataract.

The early history of intraocular lens implantation was fraught with problems. Such complications as dislocation, corneal edema, persistent inflammation, secondary glaucoma and endophthalmitis were disturbingly common. Improvements in the finishing, polishing and sterilization of implant lenses and in the surgical techniques have greatly reduced these complications. The specter of serious, unpredictable long-term complications has not materialized although a few lens styles have been associated with late corneal decompensation.

In 1978 the Food and Drug Administration (FDA) classified all intraocular lenses as investigational devices. More than 1 million lens implantations have been monitored. Based on the data from the first 50,000 lenses, the FDA has approved several lens styles from a variety of manufacturers.

Presently, the posterior chamber lens styles are the most popular. Anterior chamber lens styles are also used frequently for both primary and secondary implantations. The use of iris-supported lenses has declined substantially.

In 1982 about 70% of the patients in whom cataract extraction was done in the United States received an intraocular lens implant. Lens implants may now be considered in any cataract patient who has an otherwise healthy eye. Implantation is especially indicated when a patient is not likely to tolerate a contact lens or an aphakic spectacle. An increasing number of patients are receiving "secondary" implants when trials with aphakic contact lenses or spectacles do not prove satisfactory.

Controversy still exists regarding the lower age limit for implantation. Contraindications have been diminishing as experience has improved. Caution is advised in patients with only one eye, severe myopia, uveitis, glaucoma, diabetic retinopathy, corneal endothelial dystrophy or other progressive ocular diseases. Although intraocular lens designs and surgical techniques are still evolving, the improvements accomplished over the past two decades have made lens implantation safe and effective for most cataract patients.

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Ophthalmic Genetics: A New Synthesis

As INFECTIOUS DISEASES such as rubella have been brought under control with improved public health measures and immunizations, genetic factors have become increasingly important causes of both congenital and acquired eye diseases, particularly in the pediatric age group. Although accurate statistics are not available in the United States, it is estimated that at least 50% of new cases of legal blindness (20/200, or less than 20 degrees of peripheral vision) in the pediatric age group can be attributed to genetic causes; the economic and social consequences of this visual impairment are devastating. An ophthalmologist assumes a central role in identifying the cause of such visual handicaps and may assist pediatricians or geneticists in establishing a diagnosis in an otherwise perplexing patient. Referral is of particular importance in the detection of unilateral visual impairment, as a child with good vision in one eye may be asymptomatic. The eye is affected relatively early in the course of many genetic metabolic diseases and an ophthalmologist may be the first physician consulted. For example, patients who have Spielmeyer-Vogt disease, a lipopigment storage disorder, may have decreased central vision and ophthalmoscopic findings compatible with juvenile macular degeneration; progressive mental deterioration and visual impairment ensue. For some disorders, such as mannosidosis and Fabry's disease, the ocular manifestations are unique and diagnostic.

The hereditary bases of diseases that affect the eye include all three broad categories: chromosomal aberrations, single gene mutations consistent with Mendelian inheritance patterns and multifactorial inheritance. Some hereditary disorders that affect the eye have multiple genetic causes. The incidence of retinitis pigmentosa is about 1 in 3,000, much more common than would be expected from a disease caused by a single gene. Inheritance follows autosomal-dominant, autosomal-recessive and X-linked patterns. Although retinitis pigmentosa was thought to be a hereditary disease in all cases, a recent analysis of a large group of patients using segregation analysis, a complicated mathematical model, showed that some forms are not hereditary; the responsible environmental factors are not yet known.

The story of retinoblastoma has recently been unraveled. Strong evidence implicates a gene for this ocular malignancy on the short arm of chromosome 13 near the gene for esterase D, an enzyme that is unrelated to retinoblastoma. It is now believed that both the hereditary and the chromosomal forms of the disease are caused by an abnormality of the same gene. Neither the DNA sequence nor the biologic function of this oncogene has been identified.

The precedent for bringing a lawsuit for a wrongful birth has been set in the state of California by several cases that have been decided by the Supreme Court. Ophthalmologists and other physicians should consider the possibility of genetic factors in their visually handicapped patients: geneticists are well trained to relay information about hereditary disorders and congenital malformations without imposing value judgments.

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Laser Treatment for Glaucoma

THE OPHTHALMIC LASER was one of the earliest clinical applications of laser technology to medicine. Treatment of ocular disease primarily involved laser therapy for diseases of the macula, retinal tears and diabetic retinopathy. More recently, the argon laser has become a significant aid in the surgical treatment of both open-angle and closed-angle glaucoma. By using the laser, the number of patients requiring a conventional glaucoma operation has been reduced along with the associated complications, prolonged hospital care and inconvenience to patients and physicians.

Argon laser trabeculoplasty is the procedure used for open-angle glaucoma. Currently, it is the primary procedure of choice when the intraocular pressure cannot be adequately controlled medically. By placing small laser burns in the trabecular meshwork of the anterior chamber, the outflow facility of the eye increases and the intraocular pressure decreases. The 50 micron-sized burns are not full thickness, but cause stretching of the adjacent trabecular meshwork and enlarge the outflow channels. The surgical procedure is done on an outpatient basis, requires only topical anesthesia and is associated with minimal patient discomfort. Long-term follow-up is not available as the procedure first became a clinical research tool in the middle and late 1970s; however, three-year follow-up studies show an average decrease in intraocular pressure of 6 to 8 mm of mercury.

The optimal number of burns, their exact placement and the extent of the angle area to be treated are issues still under investigation.

For surgical management of cases of narrow (occludable) anterior chamber and narrow-angle glaucoma, argon laser iridotomy has replaced surgical iridectomy in all but the most difficult cases. This procedure is also done on an outpatient basis with topical anesthesia and minimal discomfort. In laser iridotomy, light is absorbed by the melanin pigment in the iris. The heat generated from the laser burn produces a

full-thickness iris hole and allows aqueous humor to flow from the posterior to the anterior chamber of the eye. This relieves the pupillary block mechanism of narrow-angle glaucoma. After laser iridotomy the intraocular pressure is elevated temporarily from the dispersion of pigment into the anterior chamber. This elevation is usually mild and can be controlled medically. Some iris colors increase the difficulty of the procedure, particularly very light blue and very dark brown irides. Occasionally a full-thickness hole cannot be produced, requiring a repeat laser attempt or a conventional surgical iridectomy. Lens burn, mild iritis and corneal burns have been noted.

Argon laser trabeculoplasty and argon laser iridotomy are acceptable modes of surgical therapy, and have been valuable adjuncts in the clinical management of glaucoma.

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Corneal Preservation

THE COLLECTION, evaluation and preservation of viable corneal tissue for purposes of transplantation are the major functions of a modern eye bank. Prospective donors are carefully screened by eye bank personnel for transmissible diseases or disqualifying ocular disease that would contraindicate their use as graft material. Tissue is then removed from a donor by enucleation of the whole globe or by excision of the cornea and a rim of sclera from the globe in situ within six hours after death.

Corneal tissue is evaluated by morphologic examination of the cornea with a slit-lamp biomicroscope or by using more recently developed specular microscopy for examination and counting of corneal endothelial cells.

Tissue preservation is necessary to allow for preparation of patients and transport of tissue and is accomplished by one of three methods: (1) moist-chamber storage of the whole globe, (2) intermediate cold storage in tissue culture medium and (3) long-term preservation in organ culture systems.

Corneas preserved as part of an intact globe in cold, moist-chamber storage must be used within 24 to 48 hours after death (short term). Storage of an excised cornea in modified tissue culture medium (McCarey-Kaufman [MK] medium) at 4°C extends tissue viability to 96 hours postmortem (intermediate term). More recently developed preservation of the delicate corneal endothelium in organ culture at 37°C has extended endothelial viability in storage to several weeks (long term). Most eye banks currently use intermediate-term preservation (MK medium).

Meticulous care to details of aseptic technique and preservation of endothelial integrity have enabled eye banks to provide excellent tissue to transplant surgeons and their patients. Medical standards for the qualifications of eye bank personnel, screening of appropriate donors, techniques of tissue handling and methods of corneal preservation have been determined by the Eye Bank Association of America.

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Extended-Wear Lenses and Corneal Infections

EXTENDED-WEAR soft contact lenses have been approved for use in both myopic and hyperopic patients for several years. While some of the initial concerns involved the ability of the cornea to metabolically tolerate these lenses over longer periods, this has not proved to be of major consequence. Rather, more significant problems have occurred in two other areas—lens maintenance and infections. Some patients must remove their lenses to eliminate films and deposits. Unfortunately this is especially true in older patients who would benefit most from limited handling. While this problem provides a certain inconvenience, it is of no serious medical consequence.

Infection, however, may be the cause of permanent visual loss. It has been shown that merely having an extended-wear lens in place does not seem to change the normal bacterial flora of the eye. Nevertheless, corneal ulcers can and do occur, resulting in corneal scarring. Whereas these infections are uncommon, they occur when least expected and without warning. One would think that decreased handling would result in reduced incidences of infection, but this is apparently not the case. They are probably related to oxygen compromise. Continual administration of antibiotic drops is not justified, although hygiene is important to maintain. It is vital, however, that a red eye in a patient using extended-wear lenses be reported to that patient's ophthalmologist immediately.

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YAG Laser Posterior Capsulotomy

CATARACT OPERATIONS and intraocular lens implantation have changed dramatically in the past decade. Extracapsular surgical treatment in which the posterior capsule of the lens is preserved is popular because of the possible benefits of improved lens fixation and reduced risk of retinal detachment and cystoid macular edema. In 30% to 50% of cases, the posterior capsule opacifies in the years following a cataract operation. Until recently treatment of opacified capsules was limited to invasive procedures to open the membrane.

Working simultaneously and independently, Aron-

Rosa of Paris and Fankhauser of Bern, Switzerland, developed short-pulse high-power neodymium-YAG (yttrium-aluminum-garnet) lasers for use in ophthalmology. These lasers use extremely high-power densities that cause optical breakdown, leading to a mechanical separation of tissue. These instruments were quickly adapted to the problem of an opaque posterior capsule and are now widely used for noninvasive laser procedures to open these membranes.

Laser operations for secondary capsulotomy have several advantages over invasive procedures. The laser procedure is totally noninvasive, eliminating the risk of infection. The opening in a capsule can be designed more precisely than a surgical capsulotomy. The treatment is painless and is done on an outpatient basis, reducing cost and patient discomfort. Complications have included a temporary increase in intraocular pressure after capsulotomy and damage to lens implants. Lens implant damage has had only minor effects on visual acuity and can be minimized with proper treatment technique and lens implant design. The increased intraocular pressure problem is currently being investigated.

Other uses of the YAG laser include iridotomy and vitreous strand cutting, which are promising applications but have not achieved the widespread acceptance of posterior capsulotomy. Posterior capsulotomy remains under the control of the Food and Drug Administration, with the YAG laser being an investigational device.

Confusion persists among lay persons and medical professionals concerning "laser cataract surgery." The YAG laser can open the opaque posterior capsule after a cataract operation, but no laser treatment can remove a cataract.

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Macular Function Testing

In patients whose eyes have such dense cataracts that the retina cannot be seen, the functional state of the macula must be evaluated so as to provide the most accurate prognosis concerning postoperative visual acuity. Instruments recently developed to predict more accurately the visual outcome following a surgical procedure include the blue-field entoptoscope, interferometers that use either incandescent or laser light and the potential acuity meter.

The blue-field entoptoscope is a light projector into which a patient peers. The light is deep blue and of varying intensity. A patient with a normal macula will report briskly moving particles in a fairly regular pattern, evenly distributed over the entire field.

Interferometric fringe patterns are also used. They are generated from an incandescent light source or a helium-neon laser. Interference fringe patterns are produced that are projected on the retina as a series of parallel lines of varying coarseness. The finer the perceived fringe, the better the predicted visual acuity.

The potential acuity meter is the most recent arrival of these new instruments. This is an elegant Snellen's vision chart projector, which is attached to the slit lamp. By aiming it at the clearest portion of the cataract and asking the patient to search around for the clearest view, a formal vision chart can be clearly projected onto the macula.

In very dense cataracts the images to be seen with these instruments often cannot be perceived even with a normal macula, and their predictive value is much less accurate. In moderately dense cataracts a good preoperative measurement with any of the above instruments offers a greater assurance of good postoperative visual acuity.

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Editorials

Health Care and Not Enough Dollars

For the first time in our history we find ourselves in a situation where there simply are not, and never will be, enough dollars to provide all the health care that our citizens have been promised as a matter of right. Both the public and private sectors of society have recently rebelled, and will no longer pay the presently escalating cost of equal access to high quality health care for all. For the time being at least, this promulgated right for all our citizens appears to have been tacitly abandoned. The harsh realities of why there are not enough dollars, why there never can be and what might realistically be done about it seem so far not to have really entered the public consciousness.

The significance of several progressive and irreversible pressures on the health care dollars needs better recognition. Advances in medical science and technology will inevitably continue and so will the demands to do more things for more people at greater cost. The population itself is growing and will continue to grow. Even more important, more people are living long enough to become elderly, and the elderly are known to require significantly more health care. And the moral commitment to access and quality of care for all remains with us. It is shared by the medical profession and the public alike, and is almost certain to be supported by whatever legal actions are necessary and by the courts. Pressures such as these are real and unremitting for the foreseeable future. They are among the reasons why there are not and never will be enough dollars for health care.

These ever-rising costs have been of serious concern for more than a decade. Various remedies have been tried which need not be recounted here. None of them have had much effect. Even the progressive, and some might say irresponsible, underfunding of entitlement programs, including Medicare and Medicaid, has had the effect of transferring actual but unmet costs to the private sector, thus solving little if anything.

There is now a concerted effort under way to introduce competition into health care on the theory that this will reduce costs. This is being vigorously promoted by all branches of government and in the private sector as well. But it is by no means certain that competition will reduce costs. What is happening is that the competitive approach is pitting doctor against doctor, hospital against hospital, hospital against doctor and doctor against patient. It seems more than likely that whatever cost savings or better services that may be achieved by this kind of competition may be more or less offset by the many health care dollars that will be siphoned off to finance just this competition. The elaborate marketing, defensive and adversarial activities that are necessary for survival in any such competitive environment are costly, and the dollars must come out of someone's health care pocket. In short, dollars that could and should be used for health care are having to go for other purposes.

If the assumption is correct that because of the irresistible pressures mentioned earlier, there will never be enough dollars for health care (at least in the way we customarily render it), then in the opinion of this writer a different approach to fitting the available dollars to the needs is necessary. It is suggested that at the very least such an approach would focus on (1) making as many of the "not enough" dollars as possible available for "hands-on" health care, (2) using these in terms of truly cost-effective diagnosis and treatment and (3) bringing sensitive caring at the physician-patient interface more closely into the economic equation. This would suggest something like the following, at least as a point of departure for thinking about some new approach:

- The competitive and adversarial approach to health care and many of the regulatory cost-control measures now in use are wasteful of many scarce health care dollars. To the extent possible these should be retrieved, conserved and used to provide needed health care. This suggests a return to a more cooperative approach by all the parties concerned to make the best use of as many dollars as possible in the interest of patients and their actual needs for care.
- To improve economic efficiency in the use of limited health care dollars serious attention should be given to identifying which diagnostic and therapeutic procedures are worth their cost and which are not, and to matching the most cost-effective level of care to the needs of each patient. For example, some treatment modalities are even now known to be ineffective, and greater availability of home health services might reduce the need to use more expensive facilities in many instances.
- At the physician-patient interface there will need to be a new understanding and acceptance of the fact that it is often not necessary or best to do everything possible in every circumstance. Genuine caring and greater emphasis on the cognitive functions of a physician in an individual case can be brought into the economic equation, and in many instances much unnecessary expense avoided. Not doing everything possible for everybody all the time (especially extreme measures in medically hopeless situations) will require some turnaround in present-day attitudes and probably some relief from present-day pressures on physicians to practice as defensively as they do now.

The medical profession and the public are both reluctant to abandon the principle of equal access to high quality care for all. Rationing or denial of care is

as unpalatable now as it ever was. At the very least it would seem reasonable to try to fine tune the use of the dollars that are available and to get the most out of them for truly needed, efficient and effective care for all.

MSMW

Antibiotic-Associated Colitis

THE COLON is a confusing and complicated anaerobic niche. It has been "guesstimated" that some 200 to 400 species of bacteria constitute half the organisms enumerated in this locale. The other half are yet to be named and the role of colonic anaerobes is still not well understood. These organisms are believed to be important in the degradation of many substances found in the succus entericus, such as enzymes, hormones and drugs, and in the metabolism of bile acids and vitamin K. By-products of this fermentative factory are primarily feces (composed of bacteria, water and undigested food) and flatus. It is no surprise then that antibiotics effect profound alterations in this milieu, which is the subject of the article presented in this month's journal by Stergachis and colleagues.

The incidence of antibiotic-associated colitis was analyzed from 1977 to 1980 for a large health care group located on Puget Sound. Approximately 280,000 patients were enrolled in the plan, and from previous studies it appeared that about 98% or more of all written prescriptions were fulfilled in this system. Thus it is likely that the authors had accurate data concerning the incidence of this disease associated with antibiotic therapy. In a group of 344 patients who were found to have colitis on discharge from their hospitals, antibiotic-associated colitis was diagnosed in four. It is unfortunate that the authors did not have the technology available to do either stool cultures or analyses for fecal toxins of *Clostridium difficile*. The clinical cases presented by the authors, however, do appear typical for clostridial enterocolitis.

In multiple studies *C difficile* has now been identified as the most common cause of antibiotic-associated colitis.[1] In several studies this organism has been found in from 3% to 6% of stool specimens (without toxin present) of normal humans. Apparently almost every antibiotic available on the market has induced this disease.[2] Therefore, colitis should be recognized as a complication of all antibiotics. This organism is also one of the first anaerobes to colonize the gastrointestinal tract of newborns, but does not produce any disease in this age group. The reasons for this paradox need further investigation.

The article also addresses what I believe is a realistic incidence of this disease (1.6 to 2.9 cases per 100,000 cases of patients exposed to antibiotics). These figures are primarily for oral therapy. When clindamycin was noted to be the major offender of this disease in 1977, clostridial colitis was misnamed "clindamycin colitis." At that time the manufacturer of clindamycin found an incidence of colitis of one case per 100,000 to 150,000 patient users. In-hospital patients receiving parenteral therapy may be more sensitive to colonization with *C difficile*, as this organism can be found in hospital environments,[3] and the infective dose for humans may be very small while they are taking antibiotics. In experimental hamsters, as few as one *C difficile* organism administered orally can precipitate fatal colitis if the animals are pretreated with an antibiotic to reduce colonization resistance within the gastrointestinal tract. It should also be recognized that this disease can be attributed to risk factors other than antibiotics, such as cytotoxic cancer chemotherapy, diabetes mellitus or hepatic failure.

The case histories presented in this month's journal also reiterate several clinical messages.[1,4] The first is that very trivial infections (such as toe infection, epididymitis, prostatitis and acne) treated with antibiotics can be associated with the occurrence of colitis. Second, the antibiotics were given orally and were commonly used ones such as dicloxacillin sodium, tetracycline and ampicillin. The symptoms of diarrhea can occur anywhere within a few days of initiating antibiotic therapy or up to six weeks after stopping antibiotics. In some patients, if the antibiotic therapy is continued, the diarrhea can be chronic, as was seen in one of their patients who continued to receive tetracycline and had five weeks of associated bloody diarrhea. While the authors found no cases attributable to the use of amoxicillin trihydrate, cephradine, erythromycin or penicillin, these antibiotics have been implicated with causation of colitis.[2] The authors also found no cases of colitis associated with the topical use of clindamycin in more than 1,500 cases. This is a popular regimen for acne that is believed effective. As the authors indicated, there have been a few cases of colitis seen with topical clindamycin because it is absorbed across the skin and can achieve levels within the colon sufficient to alter gastrointestinal flora.

Three of the four cases presented by Stergachis and co-workers were treated by stopping the precipitating antibiotics, and the fourth was treated with vancomycin. If a patient with colitis does not respond to elimination of the antibiotic, one can then administer orally and in divided doses (every 6 to 8 hours) either vancomycin (500 mg per day), metronidazole (1,000 mg a day) or bacitracin (100,000 units a day). Whereas the relapse rate following treatment with the first two agents is around 10% to 12%, almost all patients improve with a 5- to 7-day course of one of these three antibiotics.[5] Metronidazole has recently been shown by Teasley and associates to be as effective as vancomycin and is appealingly cheaper.[6]

In summary, their article addresses the incidence of a serious and sometimes morbid lesion in patients. The key point for all physicians is that all patients receiving antibiotics, particularly those who take them on a long-term basis, should be advised as to the complication of colitis. Also, patients should be queried by physicians if given long-term antibiotics for the presence of five or more loose stools a day, or stools that contain blood

or mucus. These are useful signs of possible colitis that should dictate other studies, or at least stopping the inducing antibiotic regimen.

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How Much Toxicity Is Necessary?

SINCE THE FORMAL recognition of the specialty of medical oncology, and the provision of resources through the legislation of the National Cancer Act in 1971, considerable progress has been made in the management of neoplastic disease in the United States. Now almost 50% of patients with serious forms of cancer survive for five years, and many are regarded as cured. For patients younger than 45 years of age there has been a definite reduction in cancer mortality rates. To a large extent, this can be ascribed to the development of effective forms of cancer chemotherapy. The notable advances in the management of diseases such as acute lymphocytic leukemia, Hodgkin's disease and testicular cancer have, however, come at some cost, in particular in the form of clinical toxicity of the treatment used. In general, antineoplastic agents have a relatively low therapeutic index, exerting their cytotoxic action through a direct attack on either DNA or its synthesis. Their ability to discriminate efficiently between normal and target tissues is somewhat limited. As a consequence, a wide spectrum of adverse reactions is expected and has become generally accepted by the profession and the public as an unfortunate but necessary concomitant of treatment. The problem is further compounded by the fact that modern anticancer treatment rarely involves the use of a single cytotoxic agent; more commonly, cancer is treated with a combination of drugs—with overlapping toxicity for a single organ system—or with a combined modality approach in which anticancer drugs are given along with radiation therapy.

In this issue of the journal, McDonald and Tirumali present a comprehensive review of the many forms of toxic reaction of the gastrointestinal tract that are potentially associated with treatment with antineoplastic agents. This list of adverse reactions is impressive but must be placed in some context in regard to actual incidence. A serious or even clinically detectable hepatotoxic reaction, as an example, is unusual and rarely limits treatment. In addition, there is a considerable and largely unexplained variation in the degree of toxic effects experienced by patients treated with an identical regimen, with some patients having no effect while others are devastated. For the more subjective reactions, the frequency and magnitude of response may be influenced by a patient's preconceptions regarding chemotherapy, as well as the extent of preparation they have received and rapport they have established with the treating physician. Nevertheless, the more common toxic effects—anorexia, nausea and vomiting—can have serious consequences on the effectiveness of overall management. The reaction may be so severe as to limit a patient's acceptance of further, and possibly curative, treatment. Equally important, there can be a deleterious effect on patient nutrition, which compounds the all-too-frequent state of malnutrition that accompanies advanced cancer and the associated cachexia syndrome.

During the past seven years our understanding of the importance of toxic reactions of the gastrointestinal tract has become more focused and enlightened. This has resulted in the development of more effective antiemetic agents such as tetrahydrocannabinol and metoclopramide hydrochloride, as well as the establishment of nutritional supportive care as an essential component of overall management. In many cases a physician has a relatively broad range of chemotherapeutic options to select from; within limits, toxicity can be purposely reduced through the appropriate choice of drugs, dosage and schedule. This also assumes that a physician has accounted for the large number of additional variables that have been recognized to influence the risk of toxic effects, such as a patient's age, nutritional status and extent of prior therapy, and the clinical pharmacology of the drugs to be used. The medical and ethical difficulties encountered in patient selection and in determining a safe and effective dose for an individual case cannot be underestimated.

A critical question, and one fraught with considerable controversy, is what degree of toxic effects, if any, is required to insure that an optimal therapeutic dose has been administered. Under unusual circumstances, best exemplified by the current treatment of acute myelogenous leukemia, profound if not life-threatening hematologic and gastrointestinal toxic reactions are unavoidable. For most solid tumors, however, I strongly believe that serious adverse gastrointestinal reactions are not only unnecessary, but possibly avoidable. For example, many women who receive full-dose adjuvant chemotherapy following a mastectomy experience a stimulated appetite and have impressive weight gain during the 6 to 12 months of treatment. Studies using animals and clinical experience have shown that the current armamentarium of anticancer drugs has a definite but limited capability to select out and destroy cancer cells. This process is strongly influenced by complex mechanisms of neoplastic cell resistance and normal tissue tolerance. To simply increase drug dosage has rarely been shown to result in a measurable positive

increment of tumor response, relative to what is achieved with the accepted "conventional" dose range. Rather, such an exercise has been consistently associated with greater toxicity, with a possible negative impact on patient survival. This therapeutic philosophy is not universally shared by all respected oncologists, particularly those schooled in an earlier era when a serious toxic reaction was regarded as the only endpoint for determining that a biologically active dose had been administered. The concept of high-dose treatment is still being actively explored in studies using autologous bone marrow stem cell rescue, and I await the results of these trials before revising my thinking on this matter.

The degree of selectivity that can be achieved should not be underestimated. The gastrointestinal mucosa, like the bone marrow, is in a constant state of cell renewal. On this basis, and from data derived from animal toxicology, crypt cells have been regarded as highly vulnerable to chemotherapeutic attack. The human small intestine is in actuality remarkably resistant. In the study of Smith and co-workers described in the review, they examined the effect on the small intestine of combination chemotherapy, of the type that is commonly used in the treatment of Hodgkin's disease, breast cancer and gastric cancer.[1] There was no influence on the absorptive function of the small bowel, as measured by standard clinical criteria, and mucosal morphology remained intact aside from a transient reduction in mitotic figures. Obviously, this reserve capability can be overridden if one purposely chooses to use extraordinary doses.

During the past decade we have witnessed encouraging and in some cases dramatic improvements in the life expectancy of selected groups of cancer patients. These have largely come as a direct result of the development of effective forms of antineoplastic chemotherapy. There is a basis for anticipating that conceptual and technologic advances in the fields of oncogene research and immunology will result in less empirical and more selective forms of cancer treatment in the future. Nevertheless, it is safe to say that the current established forms of treatment and their associated gastrointestinal toxic effects will continue to dominate during the next five years. One of the major challenges in the field of oncology during the 1980s is to not only improve the therapeutic efficacy of existing anticancer treatment, but to prospectively design and evaluate drugs, biologics and regimens that focus on the critical issue of quality of life.

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Case Reports

Nitrofurantoin-Induced Cholestatic Hepatitis From Cow's Milk in a Teenaged Boy

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ACUTE HEPATOTOXIC reactions to nitrofurantoin, a frequently prescribed antibiotic, are rare.[1,2] We report a case of nitrofurantoin-induced cholestatic hepatitis in which the offending agent had been unknowingly ingested in cow's milk.

Report of a Case

The patient, a 16-year-old male high school student was admitted to Longmont (Colorado) United Hospital in late May of 1981 because he had had epigastric and right upper quadrant pain for three days. The pain was aching and cramping and associated with nausea and vomiting. One day before admission, an erythematous rash involving the palms and soles developed. On the day of admission, he noticed jaundice and had the onset of fever and chills.

The patient lived on a small farm in northern Colorado. He said he had not had contact with rodents, insect bites nor had he drunk untreated water. He consumed no alcohol and did not take prescription, over-the-counter or illicit drugs. No household contacts or friends were jaundiced, and he had not left the local area within the past year. He had no medical history of serious illness, hospital admissions or transfusions.

On physical examination, he appeared thin and jaundiced. His blood pressure was 110/80 mm of mercury, pulse rate was 96 and oral temperature 38.3°C (100.9°F). The sclerae were icteric; there was no conjunctival injection. The skin was icteric and there was a maculopapular eruption involving the skin of the soles and palms. The oral mucosa appeared normal. Examination of the heart and lungs elicited no abnormalities. The abdomen was flat and bowel sounds were normal. The liver margin was palpable at the right costal margin on deep inspiration; its edge was rounded, firm and tender; the spleen was not palpable. Urogenital, neuromuscular and joint examinations showed no abnormalities.

Laboratory studies disclosed the following values (normal range is given in parentheses): hematocrit, 42%; leukocyte count, 15,900 per μl, with 68% segmented and 2% banded neutrophils, 23% lymphocytes, 2% monocytes and 5% eosinophils. Serum alkaline phosphatase, 33.1 IU per liter (4.5 to 11); serum aspartate amino transferase, 68 IU per liter (22 to 47); serum bilirubin, 15.4 mg per dl, direct reacting, 8.2 mg per dl. Prothrombin time was normal; analysis of urine was positive for acetone and bilirubin but negative for albumin, blood and leukocytes. The following tests gave negative results: rapid plasma reagin, Monospot and heterophile agglutination, hepatitis B surface antigen, core and surface antibody, hepatitis A antibody, febrile agglutinins including Weil-Felix, antinuclear antibodies and *Leptospira* agglutinins. Cultures of three blood specimens taken at the time of admission grew no organisms. Abdominal ultrasound studies showed a normal gallbladder free of stones; neither the extrahepatic nor the intrahepatic ducts were dilated.

For five days after admission, the patient remained intermittently febrile with oral temperatures as high as 39.2°C (102.6°F). The skin eruption became desquamative. The leukocyte count rose to 25,400 per μl with 6% eosinophils and the serum alkaline phosphatase level reached 66 IU per liter.

A percutaneous liver biopsy was done seven days after admission. Histologic examination showed the lobular architecture of the liver to be intact. There was moderate centrilobular cholestasis with only occasional canalicular plugs; ballooning and feathery degeneration were absent. A few Councilman-like bodies were noted, some being surrounded by small aggregates of lymphocytes and histiocytes. The sinusoids contained occasional lymphocytes and eosinophils. Kupffer's cells were focally distended with periodic acid-Schiff (PAS)-positive, diastase-resistant material. Hepatocellular mitoses and binucleate cells were numerous (Figure 1). Most portal tracts were expanded by edema and a dense, predominantly neutrophilic and eosinophilic infiltrate; the neutrophils invaded many bile ducts and often were associated with epithelial necrosis and plugging of the duct lumen with eosinophilic debris (Figure 2). The limiting plates were intact. There was no fibrosis and no granulomata were found.

Because the findings of this liver biopsy were suggestive of toxic rather than viral hepatitis, the patient was requestioned about any drug ingestion. This was denied again; however, he had learned that he had consumed milk from cows that had been treated paren-

(Berry WR, Warren GH, Reichen J: Nitrofurantoin-induced cholestatic hepatitis from cow's milk in a teenaged boy. West J Med 1984 Feb; 140:278-280.)

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terally with nitrofurantoin. The cows had received nitrofurantoin parenterally during the week preceding the patient's illness and had no overt adverse reactions. Over the next few days, the patient became afebrile; the leukocyte count and serum bilirubin and alkaline phosphatase values returned to normal. The patient has remained asymptomatic for over a year.

Discussion

The incidence of adverse reactions to nitrofurantoin has been as high as 9.2%,[1] but hepatotoxic reactions seem to be rather uncommon. Thus, in a prospective study of 757 patients treated with the drug, no hepatic injury was seen.[1] In 921 adverse reactions reported voluntarily to the Swedish Adverse Drug Reaction Council, only 5% involved the liver.[2]

Acute hepatotoxic reaction of both the cholestatic[3-9] and hepatocellular type[10,11] have been described. Nitrofurantoin has also been implicated in the development of chronic liver disease[12,13] and the evidence for this has been reviewed editorially.[14] Recently, a case each of granulomatous hepatitis[15] and of focal nodular hyperplasia[16] have been ascribed to nitrofurantoin.

The present case is remarkable for three features: its occurrence in a teenaged boy, transmission of the offending agent by cow's milk and the presence of pronounced cholangiolitic lesions on examination of the liver biopsy specimen.

The age of patients who had acute liver injury due to nitrofurantoin ranged from 31 to 84 years, 80% of the patients being women.[3-11] Thus, our patient is by far the youngest and only the third male patient to have nitrofurantoin-induced hepatotoxic reaction. This presumably reflects the prescription pattern of the drug rather than any age- or sex-related difference in susceptibility.[14]

Transmission of drug toxicity by milk is a well-recognized phenomenon.[16] Nitrofurantoin achieves a milk-to-plasma ratio of 0.3 in humans.[17] By contrast, nitrofurantoin was not detectable by a bioassay of cow's milk after intrauterine administration.[18] This could be due to the insensitivity of the assay used or to inadequate bioavailability after intrauterine administration.[18]

Neither the physiochemical properties of the drug nor species differences in milk secretion suggest that nitrofurantoin is excreted into human but not cow's milk.[16] The clinical presentation of our patient with fever, rash and eosinophilia is typical of the cholestatic form of nitrofurantoin toxicity. These signs were present in 60%, 30% and 70%, respectively, of the 18 patients reviewed by Zimmerman[19] and in four, six and five, respectively, of the six patients with cholestatic hepatitis.[3,5-9] Final proof for the involvement of a particular drug in hepatotoxic reactions can often be obtained only by a positive rechallenge with the offending agent. A positive response to reexposure has been described in several instances.[3,5,9,11] However, in view of the severity of the presentation in our case and of reported fatalities,[2,7] it was felt unethical to rechallenge a young man who probably will never need to use the drug again.

The histologic picture in our case is compatible with nitrofurantoin-induced cholestatic injury. Thus, predominantly centrilobular cholestasis without feathery degeneration has been described.[3,5] Even in predominantly cholestatic liver disease, focal inflammation and mild hepatocellular damage have been seen.[3,9] An abundance of binucleate cells and increased mitotic activity (Figure 1) have also been commented on.[3] A few Councilman-like bodies are usually associated with the hepatocellular form.[11] The PAS-positive, diastase-resistant material in Kupffer's cells encountered in our case has previously been described only in a case with hepatocellular injury.[11] The pronounced eosinophilic portal and sinusoidal infiltrate, typical of drug-induced hepatic injury, has been reported in several cases.[3,9,11] An unusual feature in our case was the marked involvement of the portal bile ducts with edema, neutrophilic invasion of the ductular epithelium and, finally,

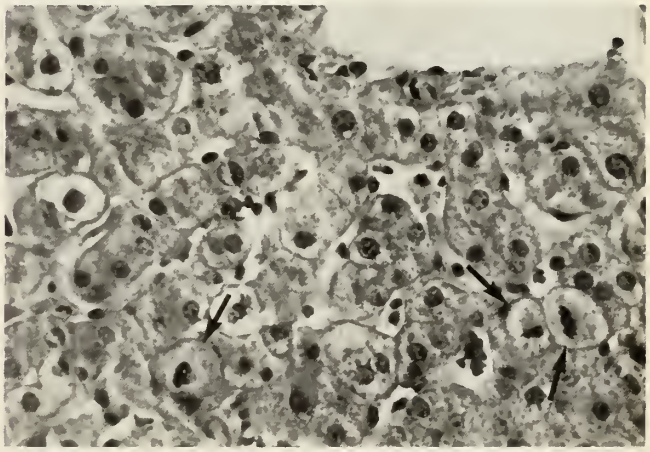

Figure 1.—A high-power photomicrograph shows three liver cell mitoses **(arrows)**, indicating regeneration near the central vein. There is no hepatocellular necrosis. (Hematoxylin-eosin stain, reduced from magnification ×410.)

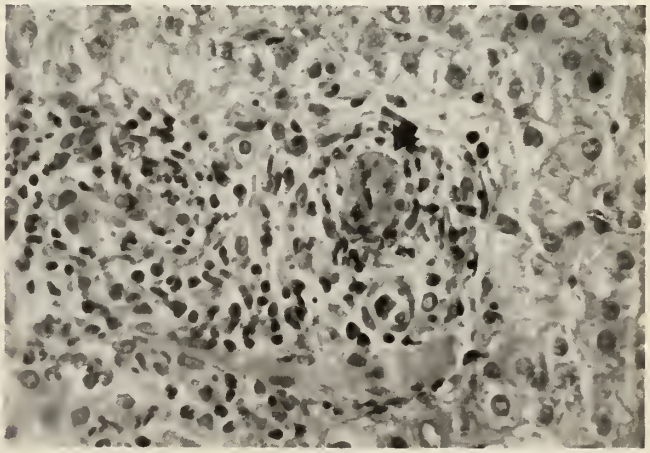

Figure 2.—A portal tract infiltrated by neutrophils and eosinophils. An interlobular bile duct is plugged by necrotic epithelial cells **(arrow)**. (Hematoxylin-eosin stain, reduced from magnification ×410.)

sloughing of necrotic cells into the ductular lumen (Figure 2). This presents a necrotizing cholangiolitis of a severity not previously recognized. Only one previous case showed some evidence of cholangiolitis but to a much lesser extent.[5]

The mechanism of action of nitrofurantoin in inducing acute or chronic liver cell injury is still debated. The presence of a variety of immunologic epiphenomena, an association with HLA-B8 in chronic hepatitis[12] and the pronounced eosinophilic infiltrate in acute hepatotoxic reaction[3] led to the postulate of an immune, possibly genetically mediated injury. The rarity of hepatocellular injury has also been taken as evidence of a hypersensitivity reaction.[19] The evidence for this has been critically reviewed and certainly is not conclusive.[14] Formation of reactive intermediates such as superoxide radicals has been found in several systems.[20,21] Furane derivatives have been found to be hepatotoxic in mice.[22] The relevance of these recent findings to toxic effects in humans is unknown.

Identifying the cause of a toxic reaction in the absence of a history of exposure can be a frustrating endeavor but, as illustrated by this case, is not necessarily a hopeless one. Cow's milk most likely served as the unsuspected vehicle for transmission of nitrofurantoin, producing a severe cholestatic hepatitis in a host of uncharacteristic age and sex for this particular drug reaction.

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Pancreatic Involvement in Hippel-Lindau Disease

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HIPPEL-LINDAU DISEASE is an uncommon autosomal dominant disease characterized by hemangioblastomas of the retina and the central nervous system. A variety of other cystic and neoplastic lesions can be found widely dispersed throughout the body, including cysts of the abdomen and neoplasms of the kidney, adrenals and sympathetic chains. Although many clinicians are aware that retinal and cerebellar lesions occur as part of the disease, the potential for multiorgan involvement is not generally appreciated. Visceral involvement, though often clinically silent, may be present.

We describe a case of Hippel-Lindau disease in which there was extensive pancreatic involvement in addition to lesions of the central nervous system.

Report of a Case

A 21-year-old Vietnamese man known to have retinal angiomatosis came to the University of California Irvine Medical Center because he had had headache, nausea, vomiting and dizziness for three weeks. He had had no weakness or sensory changes. On examination his left eye showed papilledema and increased vascularity, consistent with angioma. The patient had been observed since 1980 and had received periodic laser coagulation for preservation of his vision. He had previously undergone enucleation of the right eye because of an extensive angioma.

A computed tomographic (CT) scan of the head showed acute hydrocephalus and a large right cerebellar cyst. An angiogram showed two right-sided cerebellar hemangiomas. We excised the hemangiomas by a right suboccipital craniectomy. During the operation the surgeon found a 3-cm cyst in the posterior fossa anterior to the cerebellar hemangioma. The patient recovered from the neurosurgical procedure and his preoperative symptoms resolved.

To discover whether there was visceral involvement, an intravenous pyelogram and a CT scan of the abdomen were done. The pyelogram showed no abnormalities. A very large retroperitoneal mass could be seen on the CT scan (Figure 1). To assure that a heman-

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gioma was not present in this region we did an angiogram, which showed no vascular abnormalities in the retroperitoneum. The patient had no abdominal pain and results of blood chemistry studies were normal.

Because of the possibility of a malignancy, an exploratory laparotomy was done, which showed a multicystic pancreas with cysts involving the entire organ. The cystic changes were confined to the pancreas. There was no inflammatory reaction. A frozen section during the procedure showed benign polycystic disease of the pancreas. Permanent tissue sections showed normal pancreatic parenchyma interspersed with irregularly shaped cystic spaces lined by low cuboidal type epithelium (Figure 2).

Comment

The earliest observations of Hippel-Lindau disease predate by more than half a century the description of the syndrome as it is now recognized.[1] Von Hippel[2] is usually credited with the first clinical description of the retinal lesions, while Lindau[3] recognized the association of the retinal and cerebellar lesions with the visceral components of this disease complex.

The first description of pancreatic involvement in Hippel-Lindau disease was probably in 1884 when Pye-Smith[4] described cystic disease of the cerebellum in combination with cysts of the pancreas. Since that time lesions in virtually all other visceral organs have been described,[4] though the kidney and pancreas are the most commonly affected visceral organs.

A variety of pancreatic lesions have been reported in the literature including cysts (both simple and multilocular), hemangioblastomas, adenomas and islet cell tumors. Cysts are the most frequently occurring pancreatic lesions. Horton and colleagues reported in 1976 that 72% of the patients they studied who had this disease had pancreatic cysts at autopsy.[5] The cysts, which are usually multiple, may range in size from microscopic to large cavities. Despite the frequency of pancreatic involvement in Hippel-Lindau disease, the vast majority of such lesions have no clinical manifestations. In one study of 50 affected members in 9 families, only 2 of 23 patients who had pancreatic lesions diagnosed at autopsy had had clinical pancreatic involvement.[6]

Pancreatic disease in Hippel-Lindau disease may be manifested by exocrine or endocrine insufficiency. Bird and Krynauw[6] described a case of a patient who had glucosuria and brittle diabetes. At autopsy the pancreas was found to be completely replaced by cystic tissue. A case of a patient with steatorrhea and insulin-dependent diabetes was reported by Fishman and Bartholomew.[7] They described a slow-growing vascular tumor involving the entire pancreas and many other abdominal organs, which they concluded had led to exocrine and probably endocrine pancreatic insufficiency. Hull and co-workers[8] reported two cases in which islet cell tumors associated with Hippel-Lindau disease were found at autopsy, though there had been no symptoms indicating their presence during the lives of the patients.

Pancreatic disease may precede central nervous system manifestations in patients with Hippel-Lindau disease, as reported by Walter and Nygaard.[9] Lindau[3] believed that the finding of pancreatic cysts was almost pathognomonic of central nervous system lesions. When a clinician finds cystic or vascular tumors of the pancreas, it is appropriate to evaluate whether or not a patient has Hippel-Lindau disease.

Hippel-Lindau disease may involve many organs. The greatest morbidity and mortality are associated with retinal, cerebellar, spinal and medullary hemangioblastomas, pheochromocytomas and renal cell car-

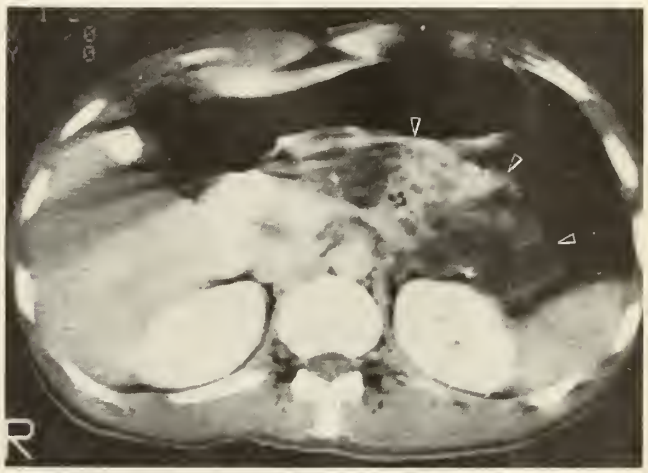

Figure 1.—Computerized tomographic scan of abdomen showing a large soft tissue mass of mixed attenuation levels (arrows). The mass extended from the upper abdomen in the retrogastric region through the retroperitoneum down to the region of the pelvic inlet. Normal pancreatic tissue was not seen. There was no evidence of any intrarenal masses or intrahepatic lesions.

Figure 2.—Microscopic tissue section of pancreas showing irregular cystic structures containing a proteinaceous fluid. The cysts are lined by a low cuboidal epithelium. There is pericystic fibrosis. Partially atrophic lobules of pancreatic parenchyma are present adjacent to the cysts. The arrow shows a solitary islet of Langerhans. (Reduced from magnification ×17.)

cinoma. The vast majority of other lesions are usually diagnosed during a surgical procedure or at autopsy. With the advent of more sophisticated diagnostic tools, many of the visceral manifestations of Hippel-Lindau disease that previously would only be found surgically may now be detected by noninvasive methods such as CT scanning.

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Chemically Induced Methemoglobinemia From Aniline Poisoning

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ANILINE HAS LONG been known to be capable of producing methemoglobinemia and a Heinz-body hemolytic anemia.[1-6] Despite decades of experience, the guidelines for therapy for aniline poisoning are not well defined and are somewhat controversial.

Chemically induced methemoglobinemia may be a life-threatening condition, requiring immediate definitive management. Yet, many substances are capable of producing methemoglobin, with varied clinical courses.[7] Similarly, the physiologic state of a patient influences both the symptoms and response to treatment of chemically induced methemoglobinemia.[2,3,8,9]

To manage chemically induced methemoglobinemia properly, a clinician must be aware of its pathophysiology, be adept with the use of reducing agents such as methylene blue, and understand specific physiochemical properties of the toxin. The following case shows the toxicity of one methemoglobin-inducing agent and the possible pitfalls and considerations in the management of chemically induced methemoglobinemia.

(Kearney TE, Manoguerra AS, Dunford JV Jr: Chemically induced methemoglobinemia from aniline poisoning. West J Med 1984 Feb; 140:282-286.)

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Report of a Case

The patient, a 32-year-old Mexican-American man, arrived at a San Diego emergency room, sweating, apneic and without a pulse after accidentally ingesting 0.3 to 0.6 dl (1 to 2 oz) of Moroso gasoline octane booster. The substance was in a 7-Up container when he mistakenly drank it. He ingested the product about an hour before arriving in the emergency room. The patient had attempted to induce emesis with sea water, but was unsuccessful.

The patient was extremely cyanotic; cardiopulmonary resuscitation instituted immediately upon his arrival successfully revived him and oxygen, naloxone and dextrose were administered. The San Diego Regional Poison Control Center was notified and the toxic component of Moroso was confirmed as 100% aniline. Arterial blood gas studies done while the patient was breathing 100% oxygen from an oxygen mask showed a partial arterial oxygen pressure (Pa_{O_2}) of 173 mm of mercury, a partial arterial carbon dioxide pressure (Pa_{CO_2}) of 30 mm of mercury and a pH of 7.39, with an oxygen saturation of 28%. (All oxygen saturation determinations were by direct measurement with an IL 282 Co-oximeter.) A methemoglobin level determination was pending at this time. Because the patient was cyanotic and unresponsive to adequate ventilatory support, and because of the history of aniline ingestion, the diagnosis of methemoglobinemia was assumed.

A 200-mg dose of methylene blue and 500 mg of ascorbic acid were intravenously administered to the patient. Ten minutes later his color improved, he became more lucid and responsive and was able to recall the accident. The initial methemoglobin level determined just before the administration of methylene blue was greater than 70%. (Quantitative methemoglobin was determined by the method of Evelyn and Malloy[10,11] as modified by Henry[12] using a visible spectrophotometer.) One hour after the administration of methylene blue, repeat arterial blood gas analysis showed a Pa_{O_2} of 205 mm of mercury, a Pa_{CO_2} of 37 mm of mercury, a pH of 7.4 with an oxygen saturation of 63% and a methemoglobin level of 34%.

ABBREVIATIONS USED IN TEXT

G6PD = glucose-6-phosphate dehydrogenase
NADPH = [reduced form of] nicotinamide adenine dinucleotide phosphate

Gastric lavage was done and activated charcoal and a cathartic were then administered. On admission, a complete blood count showed a hematocrit of 50.2%, a hemoglobin level of 17.3 grams per dl and a total leukocyte count of 11,500 per μl.

After receiving 300 mg of methylene blue and 1 gram of ascorbic acid, the patient was transferred to the intensive care unit. Over the next 12 hours, he received an additional 800 mg of methylene blue and 2.5 grams of ascorbic acid intravenously, in five divided doses. The patient appeared alert and oriented, though he had two episodes of nausea and vomiting. Despite his clinical appearance and the subsequent doses of methylene blue and ascorbic acid, the patient's oxygen saturation never exceeded 58% (Table 1). He was transferred to the University of California San Diego Medical Center for continued care.

Examination on admission to UC San Diego Medical Center about 18 hours after exposure to the aniline showed him to be alert, well developed and well nourished and appearing restless. He had cyanotic-appearing skin and dusky blue discoloration of the entire integument, nail beds, mucosal surfaces and conjunctivae. His heart rate was 90 per minute and blood pressure 160/90 mm of mercury. His respiratory rate was 24 per minute, and he had an oral temperature of 37°C (98.6°F). Laboratory studies elicited the following values: hemoglobin, 14.3 grams per dl; hematocrit, 43%; serum bilirubin, total, was 5.2 and direct was 2.9 mg per dl (normal: 1.2, total, and less than 0.2, direct); serum aspartate amino transferase, 195 IU per liter (normal 10 to 30); serum lactic dehydrogenase, 266 IU per liter (normal 25 to 195); blood urea nitrogen, 12 mg per dl (normal 8 to 18), and serum creatinine, 0.9 mg per dl (normal 0.5 to 1.5). Toxicology screening tests done on blood and urine specimens were negative for ethanol, acetaminophen, amphetamines, phenothiazines, salicylates, barbiturates, nonbarbiturate sedative-hypnotics, opiates, cocaine, antihistamines, phencyclidine and heavy metals. Results of arterial blood gas studies done while the patient was receiving 50% oxygen showed a Pao_2 of 207 mm of mercury, $Paco_2$ of 37 mm of mercury, a pH of 7.45 with an oxygen saturation of 53% and a methemoglobin level of 45%.

About 20 hours after the poisoning occurred, the patient received an additional 180 mg of methylene blue, which resulted in a reduction of the methemoglobin level to 24%. Methemoglobin levels declined spontaneously over the rest of his hospital course. His clinical course then became significant for rising bilirubin and amino transferase levels. By the third day after admission, the patient was noted to be very jaundiced and to be simultaneously having a significant reduction in his hemoglobin and hematocrit values (Table 2). Further studies showed an elevated free hemoglobin level of 722 mg per dl (normal 0 to 5), a fall in haptoglobin level to 5.1 mg per dl (normal 60 to 200) and a serum lactic dehydrogenase level of 3,630 IU per liter. A Heinz-body preparation showed the presence of Heinz bodies and spherocytes, supporting the diagnosis of a Heinz-body hemolytic anemia. On the fifth hospital day, a reticulocytosis developed, with an uncorrected reticulocyte count of 3.0%. Direct and

TABLE 1.—*Oxygen Saturation Values, Methemoglobin Levels and Doses of Methylene Blue Administered During the First 22 Hours After Exposure to Aniline*

Time After Ingestion (hours)	*Arterial Oxygen Partial Pressure (mm of mercury)*	*Oxygen Saturation (percent)*	*Methemoglobin Level (percent of total pigment)*	*Dose of Methylene Blue (mg)*
1.80	173	28.0	>70.0	...
2.08	...	...	...	200
3.00	205	63.0	34.0	...
3.58	...	...	...	100
4.08	Transfer to intensive care unit			
5.17	61	50.0	...	...
6.00	...	...	...	100
6.50	88	56.8	...	...
8.17	144	58.0	...	...
8.50	...	...	...	100
10.25	129	51.0	...	...
11.00	...	...	...	100
11.75	139	49.0	...	...
12.50	...	...	...	200
13.75	118	48.0	...	...
15.50	...	...	...	300
16.50	173	54.2	...	...
18.00	Admission to University Hospital			
18.50	207	53.1	45.0	...
20.00	302	56.8	38.0	...
20.17	...	...	...	180
21.00	...	...	24.0	...
22.00	383	71.2	20.8	...

TABLE 2.—*Hematologic Values*

Days After Ingestion	*Hemoglobin (grams per dl)*	*Hematocrit (percent)*	*Serum Bilirubin Direct/Total (mg per dl)*	*Serum AST (IU per liter)*	*Units of Packed Erythrocytes*
Initial	17.3	50.2	.....	...	..
1	14.3	53.0	2.9/ 5.2	195	1
2	13.2	37.0	3.9/ 6.7	140	1
3	11.9	31.0	3.7/ 8.4	135	3
4	11.0	28.0	.....	...	3
5	12.8	35.0	7.6/14.8	247	1
6	13.0	38.0	4.4/ 6.0	214	..
7	13.8	40.0	2.7/ 3.6	217	..
8	...	...	.....	...	..
9	12.8	37.5	1.3/ 1.9	15	..

AST = aspartate amino transferase.

indirect Coombs' tests gave negative values and a glucose-6-phosphate dehydrogenase (G6PD) screening test done on the fourth hospital day showed the presence of the enzyme. Over five days, the patient required nine units of packed red cells. A low-grade fever and sterile pyuria also developed. Empiric antibiotic therapy with ampicillin was given, but results of blood cultures were negative for any pathogens; analysis of urine showed no abnormalities. On discharge the patient's hematologic values had become stable and he was not jaundiced. He was scheduled to return for quantitative G6PD studies but was lost to follow-up.

Aniline Toxicity

Aniline has previously been implicated as a methemoglobin-producing chemical, but the mechanism of action for this response has not been fully elucidated.[7] It has been postulated that a metabolic transformation of aniline to an oxidative metabolite is necessary for the production of methemoglobin.[1,5] Phenylhydroxylamine has been identified as the possible toxic metabolite.[5]

Aniline may be systemically absorbed after either ingestion, inhalation or dermal contact.[1] The minimal toxic dose of aniline has not been fully defined, but Jenkins and co-workers[5] showed a significant elevation in methemoglobin levels in adult volunteers who were given 25 mg of aniline by mouth. The mean lethal dose of aniline has been estimated to be between 15 and 30 grams, though death has been reported after ingestion of as little as 1 gram of aniline.[1,13] Unfortunately, it was impossible to determine the amount of aniline ingested by our patient.

Ingestion of aniline may produce a rapid onset of severe methemoglobinemia as exemplified by the case presented and previously reported cases on aniline poisoning.[6,14] Jenkins and colleagues showed that a peak methemoglobin level occurred two hours after oral administration of 65 mg of aniline to one adult volunteer.[5]

Our patient appeared to be in cardiorespiratory arrest when he came to hospital, a sign consistent with a methemoglobin level of greater than 70%.[2,15,16] However, the cardiac and respiratory effects seen in this patient may have been due partly to the intrinsic toxicity of aniline and its metabolite. Evidence for such intrinsic toxicity has been found in rats and mice, in which both phenylhydroxylamine and aniline produced a ceiling methemoglobin level at doses significantly lower than the lethal dose for either substance.[17,18] Smith and associates reported that in mice that had been given aniline, only a 14% mean methemoglobin level was present at the time of death.[18] This suggests a metabolic conversion to saturation of aniline to its toxic metabolite. If metabolic saturation occurs in humans, prolonged zero-order production of a toxic metabolite would explain the persistence of significant methemoglobin levels up to 20 hours after exposure to aniline in the case reported here, despite initial reduction of the methemoglobin level by administration of methylene blue.

Treatment of Aniline Toxicity

Specific methods for managing chemically induced methemoglobinemia can be classified into five categories: (1) reduction of systemic absorption of the chemical, (2) extracorporeal removal of the chemical, (3) treatment of the "functional anemia" or the hypoxic state with hyperbaric oxygen, (4) reduction of methemoglobin to hemoglobin with the use of reducing agents and (5) replacement of methemoglobin with a functional oxygen-carrying pigment.

Minimizing absorption of aniline after ingestion consists of either the induction of emesis with ipecac syrup in a cooperative, conscious patient or the use of gastric lavage in other situations.[2] It normally takes 20 to 30 minutes for emesis to occur after administration of ipecac syrup.[19] Seizures or coma would contraindicate inducing emesis. Due to the potentially rapid onset of a severe toxic reaction with aniline and the relatively slow onset of the action of ipecac syrup, caution should be exercised with the use of ipecac syrup in acute aniline poisoning.

As in the case reported here, salt water has been shown to be ineffective and potentially hazardous if used as an emetic.[20] A widespread problem encountered with poisoning situations is the prevalence of incorrect, inappropriate and incomplete first-aid information displayed on labels of commercial products.[21] First-aid information on the label of the Moroso octane booster container did suggest the use of "strong salty water" as an emetic.

After gastric evacuation, activated charcoal and a cathartic should be administered to further facilitate removing aniline from the gastrointestinal tract.[2] Because aniline can be absorbed percutaneously, a patient's contaminated clothing should be removed and the skin decontaminated by a thorough washing with soap and water.[2]

Some physicians have tried removing aniline via extracorporeal methods.[6,14,22] The pharmacokinetic indices of aniline are not well defined, however, and the efficacy of its extracorporeal removal is uncertain.

In one case of methemoglobinemia induced by aniline and nitrobenzene, a dramatic reduction in methemoglobin levels occurred after exchange transfusion.[14] The patient had been given methylene blue during the exchange period, however, and quantitative assays for aniline were never done.[14] Therefore, it is impossible to determine the contribution of each modality to a patient's clinical improvement. Advocates of exchange transfusion assert that this procedure has a dual benefit in that in addition to removing a quantity of the toxin, a patient also benefits from the functional oxygen-carrying pigment.[7] Yet we must consider the inherent risks of transfusion, the large volume of blood necessary for this procedure in an adult and the time involved to implement the procedure.

Because aniline and its metabolites are molecules of low molecular weight we should be able to dialyze them. Hemodialysis has been used in the management of aniline poisoning.[6] In one case, after hemodialysis for 7 hours and 20 minutes, 1,300 mg of aniline was removed in the dialysate.[6] The patient's clinical state improved after dialysis, but methylene blue was administered and other supportive measures were used during the dialysis period.[6] Past experience with the use of hemodialysis in aniline poisoning, though limited, suggests that this treatment may have a role in the management of aniline poisoning. But despite the use of hemodialysis in one case, a patient died. In another case, the patient's clinical state deteriorated after dialysis coincident with a massive hemolytic episode.[6,22] Hemodialysis may be indicated for aniline poisoning if a patient's clinical state is deteriorating or not improving despite the use of methylene blue and good supportive and symptomatic management.

Hyperbaric oxygen has been recommended for the treatment of chemically induced methemoglobinemia, but there is no evidence that it is effective and there is little experience with its use.[7,14] Studies with animals using hyperbaric oxygen to treat chemically induced methemoglobinemia have shown conflicting results.[23,24]

Hyperbaric oxygen may allow oxygenation of tissues despite the lack of a normal oxygen-carrying pigment, which could provide time for reduction of methemoglobin to hemoglobin and removal of the offending chemical to occur. With aniline, however, because of its potential for prolonged production of methemoglobin and persistence in the body, hyperbaric oxygen may not be feasible.

The definitive treatment of methemoglobinemia is the use of the reducing agent, methylene blue,[1,7,25] which reduces methemoglobin levels rapidly and effectively.[1] The action of methylene blue is dependent on production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) by the hexosephosphate shunt and the activity of the enzyme, NADPH-methemoglobin reductase.[2,3,26] NADPH is necessary for the reduction of methylene blue to leukomethylene blue,[26] which is responsible for the reduction of methemoglobin to hemoglobin.[26] Hereditary enzymatic defects within the hexosephosphate shunt pathway such as a G6PD deficiency lead to impairment of the ability to produce NADPH within erythrocytes.[3] Consequently, the ability of methylene blue to reduce methemoglobin can be greatly impaired.[3] In fact, because of the oxidative potential of methylene blue, precipitation of a hemolytic episode in persons deficient in G6PD may occur.[3] In one case of aniline-induced methemoglobinemia, a Mexican-American patient with a G6PD deficiency had a negligible response to a therapeutic dose of methylene blue and a Heinz-body hemolytic episode developed.[3]

In the case reported here, the patient showed an apparent tolerance to methylene blue. Despite multiple doses of methylene blue and persistently elevated Pa_{O_2} values, the oxygen saturation failed to increase. The lack of success of methylene blue therapy in this patient could be explained in part by an unrecognized G6PD deficiency. Although we screened the patient for this deficiency, we used blood specimens drawn during an active hemolytic episode. Patients with a G6PD deficiency will show normal G6PD activity as assessed by either a qualitative G6PD screen or by quantitative serologic assay if the test sample is taken while hemolysis is occurring.[27] During active hemolysis, older erythrocytes containing less G6PD are preferentially destroyed, leaving a younger erythrocyte population with a higher G6PD content.[27]

An excessive amount of methylene blue may in itself provoke the formation of methemoglobin because of its own oxidative potential.[16] A total dose of 7 mg per kg of body weight of methylene blue has been previously recommended.[16] A dose of 5 mg per kg of body weight of methylene blue has been reported to produce an elevation of methemoglobin levels.[28] Our patient received a total dose in excess of 15 mg per kg of body weight.

Layne and Smith showed that erythrocytes lose the ability to take up methylene blue in the presence of phenylhydroxylamine.[29] They postulated that phenylhydroxylamine competitively inhibits a process in which a pentose-phosphate shunt mediates NADPH-linked methylene blue uptake by erythrocytes.[29] In the case reported, the patient may have accumulated the aniline metabolite, phenylhydroxylamine, in concentrations sufficient to competitively block the uptake of methylene blue into the erythrocytes.

Administering high doses of methylene blue will produce a blue discoloration of the skin and bodily secretions, inducing an "apparent cyanosis."[30] This may limit a clinician's ability to accurately assess the oxygenation state of a patient by physical examination. In the case reported, the apparent cyanosis noted during the patient's admission examination at UC San Diego Medical Center may have been caused by the methylene blue administered previously.

Although ascorbic acid has been recommended and used as a reducing agent in the management of acute toxic methemoglobinemia, its role is controversial.[1,3,4,7,31] Ascorbic acid has been recommended solely for use in chronic hereditary methemoglobinemia.[1] Opponents of the use of ascorbic acid for acute acquired methemoglobinemia claim that the onset of its reductive action is too slow and it offers little advantage over normal endogenous reduction of methemoglobin.[16,32] Ascorbic acid, a potential urinary acidifier, if administered to a patient with active hemolysis may increase the risk for renal toxic reaction because of an increased potential for precipitation of hemoglobin in acidic urine.[33(p1567),34(p1783)]

Guidelines for Methylene Blue Therapy

The recommended dose of methylene blue for the initial management of methemoglobinemia is 1 to 2 mg per kg of body weight, equivalent to 0.1 to 0.2 ml

per kg of a 1% solution.[2] Maximal response to methylene blue usually occurs within 30 to 60 minutes; therefore, methemoglobin levels should be monitored about an hour after administration of methylene blue.[25] Repeat doses of methylene blue should be spaced at least one hour apart and should only be given after evaluating the response to the last dose. If a patient has a negligible initial response to a therapeutic dose of methylene blue, then G6PD deficiency should be considered. It is advisable to continue to monitor methemoglobin levels even after an initial response to methylene blue because there is the potential for continued production of methemoglobin by aniline.

Continued use of methylene blue should be based on methemoglobin levels in conjunction with the clinical state of a patient. Most patients can tolerate a 30% or less methemoglobin level,[9,15,16] so methylene blue should not be routinely administered on the basis of laboratory values alone. An anemic patient, however, with a methemoglobin level of less than 30% may manifest hypoxic symptoms and consequently would benefit from the administration of methylene blue.

Methylene blue administration should be discontinued if either a negligible response or an increase in methemoglobin levels results after two consecutive doses or if the total dose exceeds 7 mg per kg.

Repeated doses of methylene blue should not be based solely on methemoglobin levels. Considering the inherent toxicity of methylene blue, a patient lacking hypoxic symptoms is a questionable candidate for this treatment.

Secondary Complications

Heinz-body hemolytic anemia has been reported following exposure to aniline.[1,3,6,14] Heinz bodies, aggregates of oxidatively denatured hemoglobin, have been observed in erythrocytes of persons with G6PD deficiency following exposure to oxidative chemicals and in normal persons after exposure to methemoglobin-producing chemicals.[35,36] Excessive doses of methylene blue—that is, more than 15 mg per kg—induced a hemolytic anemia in two infants, one of whom had a normal G6PD determination.[37] In neonates, administration of methylene blue at doses of 2 to 4 mg per kg has induced a Heinz-body hemolytic anemia.[38] This suggests that neonates are probably much more susceptible to the hemolytic action of methylene blue. Adults with a G6PD deficiency may be predisposed to a Heinz-body hemolytic anemia developing if exposed to aniline or given methylene blue.[3] The relationship between the formation of Heinz bodies and methemoglobin with a subsequent hemolytic episode is still unknown.[7] The Heinz-body hemolytic episode in this case could have been attributed to an interplay of factors. Aniline and its oxidative metabolites, excessive methylene blue therapy, or the G6PD status of the patient may have all had a role in the production of a hemolytic anemia.

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Paradoxical Embolus in Pregnancy

An Unusual Thromboembolic Event

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PARADOXICAL EMBOLISM is an unusual thromboembolic event. First described by Cohnheim in 1877[1] and named by Zahn in 1885,[2] the diagnosis has continued to bedevil physicians. Cheng[3] who collected 150 cases that had been reported in the literature found that only 20 of them had been diagnosed during life. This report documents a case of paradoxical embolus during pregnancy.

Report of a Case

A 33-year-old, gravida 2 para 0, was admitted approximately 12 hours after suffering a left hemispheric stroke. She was 38 weeks pregnant. The pregnancy had been uneventful until week 34, when long saphenous thrombophlebitis developed. The acute discomfort had diminished on a regimen of aspirin, Koch-Mason dressings and elevation of the leg. She was well on the morning of her admission. Her husband found her slumped on the floor of the bedroom on his return home in the midafternoon. At the time of her admission, she had a receptive and nominal aphasia and a dense right hemiparesis. Her pulse was regular in rate and amplitude. There were no signs of congestive heart failure and the electrocardiograph showed normal sinus rhythm. There was a diastolic murmur at the right sternal border and signs of right long saphenous thrombophlebitis. A provisional diagnosis of paradoxical embolus was made. Over the next two hours, her level of consciousness decreased and respiratory depression required endotracheal intubation. An emergency cesarean section was carried out and a healthy male infant delivered. The patient died two hours after operation.

Autopsy was performed four hours after death. There was an embolus lodged at the bifurcation of the left middle cerebral artery (Figure 1). There was a patent foramen ovale (Figure 2) without any intracardiac source of emboli. The aortic arch and carotid arteries were free of disease. The veins of the abdomen, pelvis and legs were opened and serial cuts made across the muscle bellies of both calves. The middle and upper part of the right long saphenous vein in the thigh was the site of nonocclusive thrombophlebitis with several loose organizing thrombi. The remaining veins were distended, consistent with 38-week pregnancy. The pulmonary arteries were dissected as far as possible from the hilum of each lung, then the lungs were sectioned at 1-cm intervals. There was no evidence of recent or remote pulmonary embolism.

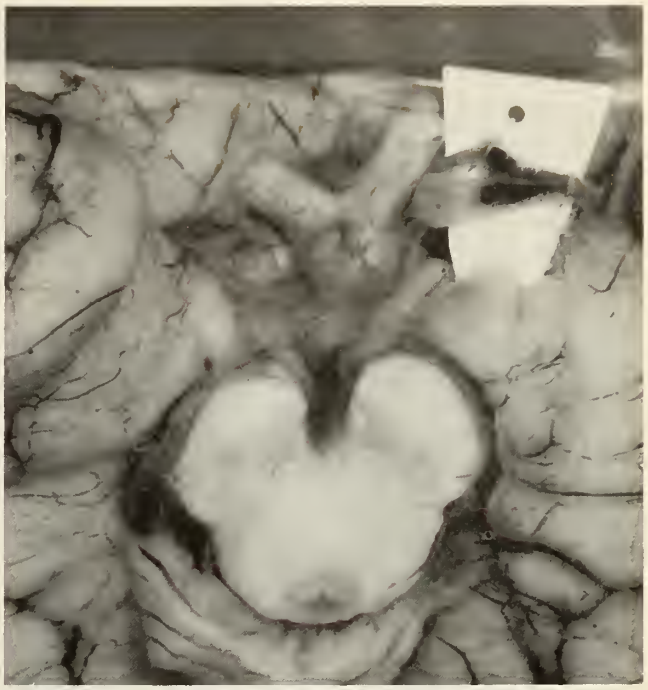

Figure 1.—The embolus is shown lodged at the bifurcation of the left middle cerebral artery.

Discussion

This case illustrates several unusual features. First, although thromboembolic events occur not uncommonly in pregnancy, and DeSwiet[4] has reported a paradoxical embolus in the puerperium, the only other report of a paradoxical embolus occurring in pregnancy is the autopsy study of Sauer.[5]

Second, the source of the embolus from the long saphenous vein is extremely unusual. The deep leg and pelvic veins, although dilated, had no evidence of any thromboses. The muscle sinuses were examined very carefully and there were no pathologic findings. The long saphenous vein, on the other hand, was the site of clinical thrombophlebitis two weeks before death and at autopsy had definite changes of thrombophlebitis in the upper and midportion of the vein in the thigh. There was no source of emboli found in the heart or great vessels and it appears that the superficial thrombophlebitis of the right long saphenous vein was the source.

Third, there was no evidence of pulmonary embolism. Previous reports[3,6-11] of paradoxical embolus have shown an almost uniform association with pulmonary embolism and raised right-sided heart pressures. Other mechanisms implicated in these reports have included

(Effeney DJ, Krupski WC: Paradoxical embolus in pregnancy—An unusual thromboembolic event. West J Med 1984 Feb; 140:287-288.)

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chronic cor pulmonale and the performance of the Valsalva maneuver.

Changes in the right and left atrial pressures during human pregnancy have not been documented. However, it is known that the total circulatory volume increases and that both atria are bigger during pregnancy.[12] The exact mechanisms of the fatal event will never be known in this case. However, it is possible to speculate that the right atrial pressure was increased toward the end of the pregnancy and that there was some flow through the defect in the interatrial septum. This hypothesis has some clinical confirmation in the physical findings of a tricuspid murmur. The inferior vena cava may be occluded by the pregnant uterus when the patient is supine, and in 35% of women the ipsilateral femoral vein will be obstructed if they lie on their side.[13] A rapid change from either of these positions would result in pronounced augmentation of the venous return from the lower limb and may produce a transient change in right atrial pressure. At the time of the embolic event, a cough, Valsalva maneuver, or even straining at stool may have caused the embolus to cross into the left side of the heart.

Figure 2.—The patent foramen ovale with normal ventricles. The atria are somewhat dilated but free of thrombus.

The extraordinary combination of clinical and pathologic findings in this case makes it unique. The baby born in tragic circumstances has grown to be a healthy child.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Screening Immigrant Children

To the Editor: The excellent study of parasites in Central American immigrant children by Sarfaty, Rosenberg, Siegel and Levin[1] presents results similar to those we have encountered in screening Southeast Asian children who were recent immigrants.[2]

As a simple rule of thumb it seems reasonable to screen all immigrant children from less developed nations for parasitism unless they have spent their lives exclusively in a middle-class urban environment. Screening with a Tb skin test and a hemoglobin determination are also suggested.

However, I would suggest this course only for those who have been in the United States for less than three years. Clinically it has been my experience that if immigrants have been in this country longer, their parasites have become commensals or have died off, especially given an improved diet in the United States. This same diet makes danger from any remaining parasites much less than on first arrival when nutrition may be compromised. Sarfaty and associates do not mention how long the children in their study had been in the United States, and perhaps they would care to comment on this point.

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Drs Levin and Sarfaty Reply

To the Editor: We would like to thank Dr Goldenring for his comments on our article. All of the immigrant children we studied were receiving their first physical examination in the United States and had been in this country for less than a year.

We know of Dr Goldenring's experience with refugees, both from personal contact and from his several publications, and it is not to be taken lightly. Our own experience, however, conflicts somewhat with his. We have continued to find a significant incidence of parasitosis in Latin American refugees even beyond three years. This has been the experience of other researchers as well.[1,2] As with most such discrepancies, the truth lies somewhere in between. It appears that certain specific parasites, such as hookworm, do indeed tend to recede after the refugee has spent about three years in this country.[3]

Further, we should add, the Central American patients we saw in our clinic in San Francisco were almost all working, middle-class and upper middle-class and yet were still quite infested with parasites.

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Opportunistic Infection, Asthma and Corticosteroid Therapy

To the Editor: A recent report in this journal[1] described the cases of two patients with asthma in whom corticosteroid therapy resulted in death by opportunistic infection: *Legionella pneumophila* pneumonia and *Pseudomonas aeruginosa* endocarditis. Our review of the literature suggests that such events are rare. We report an additional case in order to draw attention to this potential complication in asthmatic patients.

Report of Case

A 52-year-old woman with severe asthma, whose treatment included prednisone at a daily dose varying between 15 and 30 mg, was admitted to hospital with exacerbation of her condition. Because of slow improvement, prednisone administration was continued after discharge at 80 mg per day. Three weeks later she returned with bilateral pneumonia. Shock and respiratory failure developed and the patient died despite appropriate antibiotic and vigorous supportive therapy. Sputum cultures yielded heavy growth of *Nocardia asteroides* and *Pseudomonas aeruginosa.* Autopsy revealed extensive necrotizing pneumonia with the same organisms.

Comment

As noted by Leung and co-workers, most discussions of respiratory failure and death in cases of asthma

emphasize the need for prompt and vigorous corticosteroid therapy. Complications are rare with this approach, because most patients respond promptly and the steroid dose can be reduced. However, in a patient with severe bronchospasm who is slow to respond to aggressive corticosteroid therapy, the potential benefits of continued high-dose therapy must be assessed against the risks. Opportunistic infection is a risk of prolonged high-dose corticosteroid therapy in patients with asthma even in the absence of other impairments of host defenses.

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Physician Attitudes Toward Homosexuality

TO THE EDITOR: Recent attention in the United States has been focused on the life-styles of patient groups with acquired immune deficiency syndrome (AIDS). Homosexual men constitute the largest known group with the syndrome; they have experienced, at times, strong negative attitudes from those in health delivery occupations. Attitudes of physicians toward homosexual persons rarely have been assessed.[1] We studied such attitudes prior to the widespread publicity of the AIDS phenomenon.

In February 1982 questionnaires were mailed to all 2,364 members of California's San Diego County Medical Society. Of the physicians 43% (a total of 993) responded. Included in the survey were four attitudinal questions. A letter from the physician member of our survey team accompanied the questionnaire; it read in part:

Since 5% to 10% of the general population may be classified as having homosexual orientation, there are few practicing physicians who have not cared for or worked with homosexual persons, whether or not so recognized. The enclosed confidential survey is designed to assess physician attitudes toward homosexual patients and colleagues.

Our first question was "Should a highly qualified homosexual applicant be admitted to medical school?" Seven physicians in ten (69.5%) said that they should be admitted, but it seems significant that almost three physicians in ten (29.0%) had negative attitudes about the entry into medicine of "highly qualified" homosexual applicants.

Table 1 shows the results of the second question: "Should homosexual physicians be discouraged from seeking residency training in pathology, pediatrics, general surgery, psychiatry, radiation therapy?" The specialties were selected to test stereotypical concerns about homosexuals; specialties such as pediatrics and psychiatry, necessitating involvement with children or individual psyches, can be looked at in contrast to specialties such as general surgery, pathology or radiation therapy where such involvement is much more limited. Indeed, more than two fifths of the physicians thought homosexuals should be discouraged from pediatrics; almost two fifths would discourage their entry into psychiatry; slightly more than a fifth would discourage entry into general surgery, and more than a tenth would discourage entry into pathology or radiation therapy.

The physicians were even more negative toward homosexuals in the third hypothetical question asked than the second one (see Table 2). More than two fifths of all physicians would stop referrals to homosexual pediatricians and psychiatrists. General surgeons who are homosexual would find more than a fourth of their colleagues discontinuing patient referrals. Even in a restricted patient-contact field, almost a fifth would stop referring patients to homosexual radiation therapists.

A final question was asked: "How do you feel about treating homosexual patients?" Those with "no negative feelings" represented six physicians in ten (60.4%); those who indicated they were "sometimes uncomfortable" represented one physician in three (32.9%). About 7% of the physicians were "often uncomfort-

TABLE 1.—*Should Homosexual Physicians Be Discouraged From Seeking Residency Training in Any of the Following Specialties?*

	Pathology (percent)	*Pediatrics (percent)*	*General Surgery (percent)*	*Psychiatry (percent)*	*Radiation Therapy (percent)*
YES, should be discouraged	11.3	45.2	22.7	39.7	13.5
NO, should not be discouraged	88.7	54.8	77.3	60.3	86.5
TOTAL	100.0	100.0	100.0	100.0	100.0
N	(908)	(962)	(911)	(948)	(910)

TABLE 2.—*Suppose You Learned That a Physician-Colleague Is a Homosexual. Would You Continue to Refer Your Patients to This Physician if He or She Worked in Any of the Following Specialties?*

	Pediatrics (percent)	*General Surgery (percent)*	*Psychiatry (percent)*	*Radiation Therapy (percent)*
YES, would continue to refer	53.5	74.5	56.4	81.0
NO, would discontinue referral	46.5	25.5	43.6	19.0
TOTAL	100.0	100.0	100.0	100.0
N	(964)	(936)	(956)	(936)

able." Almost two fifths (39.7%) of all physicians admitted to feeling sometimes or often uncomfortable treating homosexual patients.

The preliminary results of this survey of the San Diego County Medical Society indicate a substantial prevalence of negative attitudes toward homosexual persons as both colleagues and as patients. We wonder how the recent publicity about AIDS has affected these attitudes.

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Thromboembolic Complications of Knee Arthroscopy

To the Editor: Although arthroscopy of the knee is considered to be a relatively safe procedure, reported complications have included minor articular cartilage damage, saphenous nerve injury, hemarthrosis, subcutaneous emphysema, deep vein thrombosis and pulmonary embolism. Of these, thromboembolism presents the greatest potential harm to patients. The incidence of clinical deep vein thrombosis following arthroscopy of the knee is reported to be as high as 1.6%, but subclinical thromboembolism may be much greater.[1]

Reports of Cases

We report three recent cases of thromboembolic complications following arthroscopy of the knee. The first patient was a 33-year-old man in whom pain in the left calf, swelling and pleuritic chest pain developed three days after meniscectomy. A radionuclide ventilation-perfusion scan was positive for pulmonary embolism. A 16-year-old man noted pain in his left calf four days after arthromeniscectomy, and contrast venography showed obstruction of a deep popliteal vein. And, finally, a 28-year-old man required evaluation of calf paresthesia and pain ten days following arthroscopy of the same knee. Again, a contrast venogram showed popliteal deep venous thrombosis. All patients responded quickly to anticoagulation.

It is important for physicians to realize that this potentially life-threatening complication of knee arthroscopy, deep vein thrombosis, occurs with some frequency and should be suspected promptly when calf pain occurs after the procedure.

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Individualism Versus Collectivism

To the Editor: From the manner in which you framed your understanding of how we got where we are (editorial: "America's Ways of Doing Things"[1]), I have some difficulty fitting historical events into your framework. From our long period of individualism with a free market, limited government, private responsibility and traditional social and moral values, we changed to the current collectivism with its all powerful central government and a planned economy, variously known as socialism, and a welfare state. My intent is to provide a few observations on what trends, what currents of ideologic dissemination, underlay this change. It took many decades of masterful activity by intellectuals advancing reforms to alter our traditional concepts of the proper role of government in our social order.

Following on the heels of Chancellor Bismarck's reforms in Germany and almost coincidental with Fabian socialism in England, the 1890's in the United States were productive in books on utopian thought. Following one such book—Edward Bellamy's *Looking Backward* (published in 1888 and still in print)—162 "nationalist" clubs were formed in 27 states in 1890 to discuss what was (but was denied as being) "obviously (a) socialist system." Bellamy's followers were "college professors, editors, artists and authors."[2]

The real intellectual impetus, however, occurred in 1905 with the organization of the Intercollegiate Society of Socialists. Its aims were to acquaint collegians not only with collectivist doctrines but also to influence college-bred men and women who were assuming a growing role in government. In 1921 the society was reorganized into the Student League for Industrial Democracy with the avowed purpose of "education for a new social order based on production for use and not for profit." By the 1930's, there were 125 institutions of higher learning with chapters of the organization. The graduates exerted their influence in the classroom, from the pulpit, in labor circles, media and politics. Collectivism became the dominant social creed in the universities.

(Parenthetically, much of this ideology reached the councils of the American Medical Association between 1916 and 1920. See Morris Fishbein's history of the AMA for details on the reversal [1920] of its approval of state medicine.[3] This, of course, did not occur overnight. As far back as March 25, 1893, a *JAMA* article endorsed state medicine.[4])

The majority of the key government positions were filled by President Franklin Roosevelt from the ranks of universities where the new order was taught. It is to their influence that collectivism can be attributed. To be sure, the citizenry did not vote for such a change or clamor for it; the Democratic platform of 1932 was a guide to what was intended. The platform was a complete antithesis to what followed. (It was amusing to hear Senator Goldwater's remarks about the similarities of the 1932 platform to his of 1964.) After Roosevelt's reelection in 1936, it became obvious that the "creeping

collectivism" initiated by President Hoover after the 1929 crash (but almost totally impotent from lack of political support) became a galloping force in American politics.

So, you see, long before the scientific era of medicine with its "complexities," from which you (correctly) date the government's active intrusion into medicine, there was a long period of indoctrination—from idea to law. The key to all freedom is, of course, economic freedom. And you rightly state that we do not have it in the market component of medical care. The economic underpinning of medical professionalism is being slowly eroded. There is much antibusiness indoctrination currently. But business has been fighting back, like we in medicine have for so many decades. It is also our battle.

Herbert S. Richey once asked: "Can it be that there is one thing capitalism cannot do? And that thing is, survive its own success?"[5] Isn't that what is happening to American medicine?

And the lesson for us? It is an old one, an antidote, often expressed as the "art of medicine." But what escapes our recognition is that person-to-person care is a symbolic expression of the ideologic clash between individualism and collectivism: It is absent in state medicine. It is our means of survival through the power of the people.

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Other Treatments for Herpes Zoster Neuralgia

To the Editor: The review of clinical aspects of herpes zoster by R. B. Glaser in the November 1983 issue[1] was most comprehensive, but omitted to mention a highly effective therapy for one of the more serious complications of herpes zoster, namely post-herpes zoster neuralgia. Prednisone and several other "possibly effective" internal medications were listed, but vitamin E, a simple, nontoxic agent was not included.

In 1973[2] we reported a series of 13 patients who had suffered moderate to severe pain over a period of months or years following an attack of herpes zoster, who responded to large doses of vitamin E. Of the 13 patients, 11 had had moderate to severe pain for more than six month; of these, 7 had had the pain for more than a year, 1 for 13 years and 1 for 19 years. Severity of the pain was estimated by the amounts of analgesics and sedatives required to control the pain. Nine patients experienced complete or almost complete relief, two were moderately improved and two thought they were slightly improved. Two of those who had complete or almost complete relief from pain were the two patients who had had neuralgia for 13 and 19 years respectively.

Vitamin E in the form of d, alpha-tocopherol acetate was administered in doses of 400 IU two to four times a day before meals. Inorganic iron, such as contained in reenforced white bread and many cereals, was avoided because it tends to combine with and inactivate vitamin E. Female hormones, including those in birth control pills, also inactivate vitamin E. Since vitamin E improves the tone of the heart muscle and improves glycogen storage, patients with hypertension or damaged hearts and those with diabetes receiving insulin should be started on much smaller doses, such as 100 IU once a day, which can be increased by monitoring the blood pressure or the serum glucose concentration.

The mode of action by which vitamin E relieves post-zoster pain is not known, but the high degree of effectiveness, the absence of undesirable side effects, and the present lack of adequate treatment would justify a wider use of this simple therapy.

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* * *

To the Editor: It is unfortunate that there is not a better exchange of information between various medical specialties. In Dr Richard Glaser's otherwise excellent article on herpes zoster[1] he fails to mention a modality of treatment that provides immediate dramatic relief to patients, prevents postherpetic neuralgia and is safer than high doses of corticosteroids. I am referring to the use of intralesional injections of triamcinolone into the affected dermatome.[2]

The treatment should be begun as early as possible and the patient should have the injection every 48 to 96 hours for the first week. The dose is usually 15 to 40 ml with a concentration of 4 to 5 mg of triamcinolone acetonide (Kenalog) per ml of either saline or xylocaine. Dermatologists have used this for years and those other physicians who have seen the results either learn to do it themselves or readily refer their patients. In many cases the results can be dramatic, and after using this on hundreds of patients over 15 years, I firmly believe it is a disservice to our patients not to get them started on this program as early as possible.

Also to be mentioned is acyclovir given intravenously in those cases of necrotic zoster. The anesthesiologists use sympathetic blocks with success.

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Topics in Primary Care Medicine

The Evaluation and Management of Acute Diarrhea

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

About 10% of all ambulatory visits are for acute diarrheal illnesses. Understanding their epidemiology and clinical features allows appropriate use of laboratory evaluation and rational patient management. Our discussion is limited to acute diarrheal illnesses of less than three weeks' duration.

Clinical Presentation

The differential diagnosis of acute diarrhea can be divided into the clinical syndromes of noninflammatory and inflammatory types of diarrhea. Noninflammatory secretory diarrhea is associated with cramping, bloating, periumbilical pain and large-volume watery stools. Fever and constitutional symptoms are minimal or absent. In contrast, inflammatory diarrhea or dysentery is associated with mucosal invasion and commonly accompanied by fever, other constitutional symptoms, lower abdominal pain and tenesmus. Stools are usually of small volume and often bloody or mucoid.

Causes of noninflammatory diarrhea include rotavirus, Norwalk agent, enterotoxigenic *Escherichia coli, Vibrio cholerae* and *Giardia lamblia,* as well as bacterial toxins associated with food poisoning. These organisms or toxins do not invade the mucosa but induce a secretory watery diarrhea, thus hematochezia and fecal leukocytes are typically absent. In the United States, Norwalk virus and other presumed viral agents are the most common causes of noninflammatory diarrhea in adults and produce a self-limited illness with explosive diarrhea lasting 24 to 48 hours. Rotavirus infection predominates in infants and young children and produces severe watery diarrhea of five to eight days' duration.

Travel history, recent food and drug ingestion and sexual practices are important when considering causes of diarrheas. In 25% to 50% of travelers to Mexico diarrhea develops, 70% of which is due to enterotoxigenic *E coli.* Less frequent causes of traveler's diarrhea include *Salmonella, Shigella, G lamblia* and *Entamoeba histolytica.* Although the profound secretory diarrhea caused by *V cholerae* is primarily a problem in developing nations, infection is endemic in the bayous of Louisiana and sporadic cases have been reported from these areas. Wilderness travel increases the risk of giardiasis, which is enzootic in some wild mammals, resulting in contamination of streams. Rates of giardiasis are increasing in the United States, and travel is not necessary to acquire the infection. Symptoms include bloating, cramping, periumbilical pain and foul-smelling watery stools, developing two weeks following exposure.

Foodborne diarrhea can be noninflammatory, due to bacterial toxins, or inflammatory following the ingestion of invasive pathogens. Food poisoning should be suspected when outbreaks of diarrhea occur in companions. A specific bacterial toxin may be suggested by the clinical setting. Staphylococcal toxin causes the abrupt onset of nausea and vomiting two to seven hours following the consumption of contaminated meat, poultry, cream-filled pastries or mixed salads. Abdominal cramping and diarrhea also occur. Toxicity with *Clostridium*

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perfringens requires replication of the organism, thus the onset of symptoms is delayed for 8 to 14 hours after consumption of contaminated meats. Vomiting is infrequent, and the main features include abdominal cramps and watery diarrhea that persist for 24 hours. A less common foodborne diarrhea is due to *Bacillus cereus* toxin, which can produce the pattern seen with either staphylococcal or *C perfringens* toxicity.

Inflammatory diarrhea caused by *Salmonella, Shigella, Campylobacter jejuni, Vibrio parahaemolyticus, Yersinia enterocolitica* and invasive *E coli* can also be acquired through the ingestion of contaminated food or water. Nontyphoidal *Salmonella* is the most common infectious agent identified with cases of foodborne diarrhea. Poultry, eggs and raw milk are frequently contaminated food sources. Large bacterial inoculums are required to produce illness, which is due to both bowel invasion and an enterotoxin-induced secretory diarrhea. Malaise and watery diarrhea begin 6 to 24 hours following ingestion. Fever and dysentery may also occur.

Shigellosis, often a biphasic illness, exhibits early features of a noninflammatory diarrhea characterized by the passage of voluminous watery stools. However, high fever often suggests an invasive diarrhea before the development of dysentery. This shift to an inflammatory diarrheal pattern usually occurs by the second day. *Shigella* is highly infectious, and person-to-person transmission is common. While dysentery with bloody diarrhea has traditionally suggested shigellosis, in the westtern United States, *Campylobacter* is now identified as often as *Shigella* in this setting.

Campylobacter-induced illness causes abdominal pain, diarrhea, nausea, vomiting, malaise and fever. Patients may have grossly bloody stools. Unlike *Shigella,* transmission of *Campylobacter* between adults has not been observed. The usual incubation period is two to seven days after the ingestion of contaminated materials. Most cases are sporadic, but infection has been associated with ingestion of raw milk and contact with sick pets.

Contaminated raw milk has also been implicated in outbreaks of diarrhea due to *Y enterocolitica.* Symptoms range from stools containing blood and mucus to profuse watery diarrhea. The frequency of *Yersinia* as a cause of acute diarrhea is unknown, as identification of the organism requires special culture techniques with enrichment at low temperatures.

V parahaemolyticus, a marine organism, is a major cause of outbreaks of food poisoning associated with the ingestion of contaminated seafood and shellfish. The incubation period is 4 to 96 hours. Symptoms are usually noninflammatory and include abdominal cramps, nausea, vomiting and watery diarrhea.

Medication may precipitate diarrheas. Noninflammatory diarrhea may be caused by the ingestion of stimulant laxatives or sorbitol in artificial sweeteners. Diarrhea associated with recent antibiotic use suggests the possibility of antibiotic-associated colitis. Symptoms usually include noninflammatory watery diarrhea that appears at any time up to six weeks following antibiotic therapy. In severe cases, dysentery with high fever occurs. Virtually any antibiotic can cause this syndrome. Currently, the three most commonly implicated agents are cephalosporins, ampicillin and clindamycin. Antibiotic use facilitates the overgrowth of *Clostridium difficile,* which produces a toxin damaging to the colonic mucosa.

Certain sexual practices predispose persons to selected infectious diarrheal states. Homosexual men are at increased risk for infections with *Shigella, Campylobacter, G lamblia, E histolytica, Chlamydia trachomatis, Herpes simplex* and *Neisseria gonorrhoeae.* The last is usually asymptomatic but can appear as proctitis or dysentery.

Other diseases, such as ulcerative colitis and ischemic colitis, can also present as acute diarrhea.

Laboratory Evaluation

A variety of laboratory tests may assist in determining the cause of a patient's diarrhea. The usefulness of fecal leukocyte determination, stool culture and proctoscopy varies with the clinical setting. The presence of fecal leukocytes suggests colonic mucosal invasion. A thin layer of feces or mucus is applied to a slide, mixed with one drop of Loeffler's methylene blue, sealed with cover slide and examined microscopically for leukocytes. The presence of more than five polymorphonuclear leukocytes per high power field is considered positive. Polymorphonuclear leukocytes are specific for colonic inflammation and suggest infection due to *Shigella, Campylobacter* and invasive *E coli,* antibiotic-associated colitis, ulcerative colitis and ischemic colitis. This test is not sensitive enough, however, to detect all forms of diarrhea associated with colonic invasion. For example, in one study fecal leukocytes were found in only 69% of *Shigella* infections, and similar results have been reported for *Campylobacter* infections.

Fecal leukocytes are rarely identified with noninflammatory diarrhea due to toxins, viruses, enterotoxigenic *E coli* and *G lamblia.* In antibiotic-associated colitis, leukocytes are few or absent when the process is limited but are common in diffuse disease. Likewise, *E histolytica, Salmonella, Y enterocolitica* and *V parahaemolyticus* infections produce variable findings, and the presence of leukocytes depends on the degree of colonic invasion.

Because most acute diarrheal illnesses are self-limited and caused by viruses, stool bacterial cultures should be used judiciously. Cultures are reserved primarily for the following cases: patients who have occult blood or are positive for fecal leukocytes, febrile patients (temperature above 38.3°C [101°F]), those requiring admission to hospital, food handlers and those who have diarrhea for more than one week. Identification of *Campylobacter* using selective culture medium is possible in most laboratories and should be requested

in all patients cultured. Cultures of rectal specimens for gonorrhea should be added when evaluating diarrhea in homosexual men. Follow-up stool cultures are rarely indicated except for patients with rectal gonorrhea and food handlers.

Most cases of bacillary dysentery have a similar sigmoidoscopic appearance. However, the procedure is useful in the diagnosis of antibiotic-associated colitis, amebic colitis and ulcerative colitis. When these diagnoses are suspected, sigmoidoscopic examination should be done. In addition, it is indicated for patients with culture-negative dysentery or diarrhea persisting for more than seven to ten days. Antibiotic-associated colitis is diagnosed when yellow-gray plaques (2 to 10 mm) are seen. If these findings are absent, the diagnosis can be confirmed by rectal biopsy, assessment of stool *C difficile* toxin titer or anaerobic culture of the organism.

The localized colonic ulcerations of amebiasis can be identified and suctioned or scraped during proctoscopy. Amebas tend to adhere to cotton swabs, and specimens should be obtained directly. Untrained observers may not distinguish amebas from leukocytes, and a skilled parasitologist is needed to confirm the diagnosis. Serologic examinations, with gel diffusion precipitin or indirect hemagglutination tests, are positive in 85% to 90% of patients with amebic colitis.

Sigmoidoscopy in cases of ulcerative colitis shows a diffusely erythematous and friable rectal mucosa, and evaluation for bacterial pathogens and amebas will be negative. About 10% of patients with ulcerative colitis have acute diarrhea as their initial symptom.

Examination for parasites should be carried out when undiagnosed diarrhea persists for more than a week or when travel history or sexual preference suggests increased risk for amebiasis or giardiasis. A total of three stool specimens, promptly delivered to a laboratory or collected with preservative, is optimal. Identification of ameba may be delayed for weeks by a prior barium examination, enemas, laxatives and certain antibiotics.

When diarrhea persists for two weeks, strong consideration should be given to giardiasis. Trophozoites are reliably identified in a stool specimen only during the first few days of acute illness. Small bowel aspiration with biopsy at the duodenojejunal junction may be required to recover the organism. The Enterotest, a gelatin capsule on a string, has been reported by some investigators to be as effective as duodenal intubation in confirming infection.

Barium enema examination is generally not part of the evaluation of acute diarrhea. Its major diagnostic use is in ischemic colitis, which occasionally appears as acute diarrhea. In cases of acute inflammatory diarrhea, the procedure will be irritating and carries risks of megacolon and perforation.

Therapy

The general management of acute diarrhea depends on a patient's age, underlying medical conditions and state of hydration. Therapy for noninflammatory diarrhea is directed at rehydration. Mild dehydration can be corrected with fruit juices or caffeine-free soft drinks. The absorption of sodium and water in the small intestine is more effective in the presence of glucose. Thus, more severe dehydration should be treated with a balanced glucose and electrolyte oral rehydration solution (Table 1) or an equivalent commercial preparation. Intravenous hydration is occasionally required. Beverages containing ethanol or caffeine increase intestinal motility and should be avoided. Transient lactose intolerance is commonly associated with acute diarrhea, and milk and dairy products should also be avoided.

TABLE 1.—*Oral Rehydration Solution*

One liter (1 qt*) of water containing
3.5 grams (½ tsp) sodium chloride (table salt)
2.5 grams (½ tsp) sodium bicarbonate (baking soda)
1.5 grams (¼ tsp) potassium chloride (salt substitute)
20 grams (4 tbsp) glucose (sugar)

*Approximations for home use

Symptomatic treatments of noninflammatory diarrhea can be grouped into three categories. The most controversial are the antiperistaltic agents: paregoric, tincture of opium, diphenoxylate hydrochloride with atropine sulfate (Lomotil) or loperamide hydrochloride (Imodium). These drugs decrease stool volume and relieve cramps but may impair the clearance of infectious agents and toxins. Antiperistaltics may prolong the duration of shigellosis and increase the risk of intestinal perforation in cases of amebiasis. If these drugs are used, stool cultures should be taken, and patients should be advised against their use when fever or symptoms suggesting inflammatory diarrhea are present.

A second group of medicines are the inhibitors of intestinal secretion, of which bismuth subsalicylate (Pepto-Bismol) is the prototype. When taken after the onset of diarrhea (60 ml every half hour for eight doses), abdominal cramps are relieved and bowel movements reduced in both enterotoxigenic *E coli* and viral diarrhea. These large volumes (240 ml) can be inconvenient, however, and have a salicylate content equal to 2.6 grams of aspirin.

The final group of symptomatic agents are the absorbents such as kaolin (Kaopectate) or charcoal. Although they are reported to absorb toxins and may alter the consistency of the stool, they do not diminish symptoms, number of bowel movements or fluid and electrolyte losses.

Antibiotic therapy may be indicated when specific pathogens are identified (Table 2). In general, noninflammatory diarrhea is self-limited, antibiotics are rarely required and volume repletion is the therapy of choice. However, antibiotics are generally used in the treatment of noninflammatory diarrhea due to *G lamblia* and *V cholerae*. In giardiasis, a cure rate of 95% is attributable to the use of quinacrine hydrochloride, and metronidazole is an alternate form of therapy. In the

uncommon but profound secretory diarrhea of cholera, tetracycline is the antibiotic of choice.

The prophylaxis of traveler's diarrhea and the treatment of diarrhea due to enterotoxigenic *E coli* are controversial. Although antibiotic treatment can reduce the duration of symptoms, illness is usually self-limited, and therapy may be associated with side effects and facilitate the development of antibiotic resistance. We advise travelers to avoid buffet-style meals, to drink bottled or carbonated beverages and to carry a bottle of Pepto-Bismol and a five-day course of trimethoprim-sulfamethoxazole. If diarrhea develops, early treatment with Pepto-Bismol and antibiotics will usually result in a prompt resolution of symptoms.

Prophylactic treatment is reserved for medically compromised patients. Trimethoprim, 160 mg, plus sulfamethoxazole, 800 mg, taken as a single daily dose or doxycycline, 100 mg taken twice a day, is effective in preventing most forms of traveler's diarrhea. Diarrhea developing during prophylaxis or unresponsive to treatment suggests campylobacteriosis, giardiasis, amebiasis or antibiotic-associated diarrhea and requires medical evaluation.

Inflammatory diarrhea often requires antibiotic therapy. Confirmed rectal gonorrhea always requires treatment. Recommended therapies are procaine penicillin or ampicillin, and spectinomycin dihydrochloride pentahydrate is used for penicillin-allergic patients. Tetracycline is specifically not recommended because its use for rectal gonorrhea results in a 15% failure rate.

Shigella sps are often resistant to ampicillin, and trimethoprim-sulfamethoxazole are now the antibiotics of choice. Although in vitro resistance to tetracycline is common, single high-dose therapy is often effective. Many patients with shigellosis improve rapidly before culture results are available and do not require treatment to facilitate recovery. Because the duration of shedding of this highly infectious organism can be shortened with antibiotic therapy, we choose to treat all symptomatic patients who have confirmed shigellosis.

The diarrhea associated with *C jejuni* is largely self-limited, and antibiotic treatment begun late in the course may not alter the resolution of symptoms. However, we recommend treatment of severe or protracted disease. Most strains are susceptible to erythromycin, and it is the treatment of choice. Likewise, *Yersinia*-associated colonic diarrhea is usually mild, self-limited and requires no treatment. Patients who have severe infections respond well to tetracyclines, but no studies have proved them superior to other antibiotics.

Antibiotic therapy is typically withheld in nontyphoidal *Salmonella,* as its use promotes the development of the carrier state. However, antibiotics are given for patients with bacteremia, those at high risk for bacteremia (infants, elderly, immunocompromised and sickle cell patients) and those with prosthetic devices as foci for the development of infection. When drug susceptibility is unknown, chloramphenicol is the agent of choice. Ampicillin or trimethoprim-sulfamethoxazole should be used in susceptible isolates.

Amebic dysentery requires treatment, but antiprotozoan therapy is controversial. Metronidazole remains the drug of choice for amebic dysentery in adults, with a cure rate of 90%. Some authors recommend combining metronidazole with iodoquinol. An alternate therapy for amebic dysentery is dehydroemetine dihydrochloride

TABLE 2.—*Pathogen-Specific Antibiotic Therapy in Acute Diarrhea*

Pathogen	*Treatment of Choice**	*Alternative Therapy*
Giardia lamblia	Quinacrine hydrochloride, 100 mg every 8 hr for 7 d	Metronidazole, 250 mg, every 8 hr for 7 d
Vibrio cholerae	Tetracycline, 250 mg every 6 hr for 5 d	Trimethoprim, 80 mg, plus sulfamethoxazole, 400 mg, 1 tab every 12 hr for 5 d
Rectal gonorrhea	Procaine penicillin G, 4.8 million units intramuscularly, plus 1.0 grams of probenecid	Ampicillin, 3.5 grams, plus 1.0 grams of probenecid, orally, or spectinomycin dihydrochloride pentahydrate, 4 grams intramuscularly
Shigella sps	Trimethoprim, 160 mg, plus sulfamethoxazole, 800 mg, 1 tab every 12 hr for 5 d	Ampicillin, 500 mg, every 6 hr for 5 d or tetracycline, 2.5 grams as a single dose
Campylobacter jejuni†	Erythromycin, 500 mg, every 6 hr for 7 d	Tetracycline, 250 mg, every 6 hr for 7 d or clindamycin, 300 mg, every 6 hr for 7 d
Yersinia enterocolitica†	Tetracycline, 250 mg, every 6 hr for 7 d	Trimethoprim, 160 mg, plus sulfamethoxazole, 800 mg, 1 tab every 12 hr for 7 d
Nontyphoidal *Salmonella* sps‡	Ampicillin, 1 gram intravenously every 4 hr for 14 d, or trimethoprim, 160 mg, plus sulfamethoxazole, 800 mg, 1 tab every 12 hr for 14 d	Chloramphenicol, 1 gram intravenously every 6 hr for 2 wk
Entamoeba histolytica	Metronidazole, 750 mg, every 8 hr for 5 to 10 d, plus iodoquinol, 650 mg, every 8 hr for 21 d	Dehydroemetine dihydrochloride, 90 mg a day intramuscularly or subcutaneously for 10 d
Pseudomembranous colitis†	Discontinue incriminated antibiotic; vancomycin, 125 mg, every 6 hr for 10 d	Bacitracin, 25,000 units, every 6 hr for 10 d

*Adult dosages, and all antibiotics are given by mouth unless otherwise stated.
†Antibiotics reserved for severe illness
‡Antibiotics not indicated except in special circumstances

given in conjunction with iodoquinol. Dehydroemetine is held as a second-line drug due to cardiac and neurologic toxicity.

Mild antibiotic-associated diarrhea usually resolves following the withdrawal of the offending antibiotic. However, antibiotic-associated colitis due to *C difficile* usually requires eradication of the organism. Vancomycin given by mouth is currently the treatment of choice. Relapse due to recrudescence of sporulate organisms occurs in up to 20% of patients and requires retreatment with vancomycin. Its high cost, bad taste and high relapse rate have led investigators to explore therapeutic alternatives. Orally given bacitracin and metronidazole are being evaluated for therapeutic efficacy. Controversy exists regarding the use of resins that bind the *C difficile* toxin. Recent studies suggest that the efficacy of cholestyramine resin or colestipol hydrochloride is limited only to mild illness. They should not be used in combination with oral vancomycin because they tend to bind with the antibiotic.

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Neonatal 'Brain Damage'—An Analysis of 250 Claims

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Advances in perinatal care have resulted in decreased neonatal mortality. Increasingly, damage in survivors has been attributed to alleged negligence. We analyzed the 250 claims (1957 to 1982) from one major insurance company for factors to characterize high-risk pregnancies and then to distinguish preventable from nonpreventable causes within the group. Using predetermined criteria, 77 (31%) were classified preventable, 105 (42%) nonpreventable and 68 (27%) indeterminate. Preventable actions could be attributed to family members as well as health care providers.

Twenty risk factors were significantly increased in the study group compared with those in a general population and included maternal, gestational, delivery and postdelivery risks. Furthermore, 13 of 25 factors differed significantly between preventable and nonpreventable cases. Those with significantly higher prevalence in preventable cases included prolonged gestation, the use of mid or high forceps, cesarean sections, meconium staining, low one- and five-minute Apgar scores, birth weight exceeding 4.5 kg (10 lb), poor tone, seizures and transfers to neonatal intensive care units. Increased in prevalence in the nonpreventable cases were congenital infections and malformations and the late onset of neurologic abnormalities.

These findings suggest preventive measures to reduce unwarranted litigation and certain cases of neonatal brain damage.

(Cornblath M, Clark RL: Neonatal 'brain damage'—An analysis of 250 claims [Medicine and Government]. West J Med 1984 Feb; 140:298-302.)

Recent advances in obstetric, perinatal and neonatal intensive care allow many neonates to survive who previously might have died.[1-5] To many, these new techniques have generated unrealistic expectations that every baby who survives will, in fact, be intact and develop normally. Quite to the contrary, many infants growing within a less-than-adequate intrauterine environment may be severely and irreversibly compromised. These same infants, often with genetic or congenital anomalies or intrauterine infections, frequently have additional difficulties during labor, delivery and the neonatal period.[6,7] Whereas both preventable and nonpreventable "accidents" or misjudgments can occur throughout pregnancy, especially during labor, delivery or after birth, these may or may not have been responsible for "brain damage" noted in some infants.

Furthermore, many infants and children may have neurologic deficits, such as cerebral palsy, mental retardation and seizures, from multiple causes occurring before, during and, at times, long after birth.[7]

The outcome of many of these cases of damaged infants has been attributed to deviations—often minor—in the management of labor, delivery, resuscitation or neonatal care, resulting in an increase in litigation. Because of the uncertainty as to the extent that preventable factors contributed to the cause of these adverse outcomes, a retrospective analysis of the records of 250 infants with claims of alleged "brain damage" was

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undertaken. On the basis of this analysis, their outcome was classified as preventable, nonpreventable or indeterminate. An attempt was then made to identify factors descriptive of or specific for preventability by comparing the preventable and nonpreventable groups. This report presents an approach used for classifying cases, the results of the study and its implications.

Material and Methods

Study Population and Sources of Data

All claims relating to perinatal brain damage in births that occurred between 1957 and 1982 in five states, and that were in the files of a large insurance underwriter between October 1980 and January 1983 were reviewed.* In all, 250 records were identified, including settled, active and potential claims, as well as several claims that had been dropped. Of the 250, 80 (32%) infants were born before 1976, 122 (49%) from 1976 through 1979 and 48 (19%) since 1979.

Material reviewed included prenatal obstetric office records; hospital labor, delivery and neonatal records; birth certificates; previously submitted experts' opinions, and investigative reports generated in conjunction with the insurance claims.† During the 25 years that these births occurred, both the quality and the quantity of information available improved. Even in recent years, however, the quality of information varied because the births occurred in a large variety of hospitals, including both community and university teaching hospitals. Nevertheless, data from all hospitals were included to avoid any selection bias in terms of the types of babies delivered, the types of deliveries or the types of care given. Therefore, whereas every item of information was not noted for every baby, all available information was included in the analysis.

Classification of Risks and Categories

A structured form was used for abstracting the data available and included a list of risk factors predictive of unfavorable pregnancy outcomes.[4,8,9] The factors were related to maternal demographic characteristics, to maternal medical history, to past obstetric history, to the present pregnancy, to the intrapartum course and to the sex of an infant and the neonatal course (Table 1). In addition, data concerning the father's age and occupation, a complete family history and all follow-up information were recorded.

The frequency of each of 27 risk factors noted in the 250 "brain damaged" infants was determined and compared with the expected frequency based on data from two large general populations (Table 1). The latter included information from approximately 54,000 children in the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke born between 1959 and 1966 in 12 participating urban teaching hospitals,[9] and from 3,326,632 live births based on 100% of births in selected states and on a 50% sample in all other states as published for 1977 by the Office of Health Research, Statistics and Technology, Public Health Service, US Department of Health and Human Services.[10]

The classification of preventable, nonpreventable or indeterminate was made by one of us (M.C.) after a complete review of all of the records and reports available. This judgment, on occasion, included consideration of some of the risk factors listed.

The criteria for classifying the cases as preventable, nonpreventable or indeterminate were as follows:

Preventable included actions or inactions taken by the mother, parents, obstetrician, family physician, midwife, anesthesiologist, nurses or pediatrician that clearly contributed to the neonatal course and outcome of the affected infant. Examples include

- Mother or parents refusing consent for timely cesarean birth;
- Misapplication of mid or high forceps resulting in skull fractures and aural hemorrhages;

TABLE 1.—*Frequencies of Risk Factors in "Brain Damaged" Infants Compared With Those Reported in General Population*

	"Brain Damaged" (percent)	General Populations* (percent)	Risk Ratio
Maternal			
Age ≥30 yr	24	19.0	1.3
Weight ≥91 kg (200 lb)	12	2.0	6.0†
Previous abortion‡	26	...	...
Infertility	4	1.5	2.7†
Gravida 1	42	39.0	1.1
Gravida 3 or more	25	29.0	0.9
Diabetes	2	0.7	2.9†
Current pregnancy, labor and delivery			
Bleeding	13	0.8	16.2†
Twins	7	1.5	4.7†
Breech	14	3.3	4.2†
Admission for false labor ‡	16	...	...
Gestation			
≤35 wk	17	4.5	3.8†
≥42 wk	22	7.8	2.8†
Mid or high forceps	14	8.6	1.6†
Cesarean section	35	15.0	2.3†
Cord prolapse	5	1.0	5.0†
Meconium	30	12.0	1.5†
Neonatal course			
Male sex	59	51.0	1.1
Apgar score, <5			
1 min	60	14.0	4.3†
5 min	40	3.0	13.3†
Birth weight			
≤2.26 kg (5 lb)	22	2.0	11.0†
≥4.5 kg (10 lb)	7	2.0	3.5†
Poor tone, "floppy"	31	2.2	14.1†
Seizures	40	2.5	16.0†
Congenital infection	19	1.4	13.6†
Congenital malformation	21	2.0	10.5†
Transfer to NICU‡	45	...	...

NICU = neonatal intensive care unit

*From Niswander and Gordon[9] and the National Center for Health Statistics.[10]
†$P \leq .05$ by χ^2 test for binomial distribution.
‡No comparable population data.

*Only the raw nonidentifiable data necessary for the analyses reported have been retained; all other identifying materials have been discarded (M.C.).

†We acknowledge the help and cooperation of Lissett Crenshaw, Frank P. Moffitt, Jr, and all of the insurance claims investigators.

- Pronouncing infants dead who later were revived and survived;
- Inadequate treatment of infection in one twin, but not in the other;
- Inexpert ventilatory management inducing bilateral pneumothoraces.

Nonpreventable included cases in which the untoward outcome or clinical course could not have resulted from any specific action or inaction taken during the perinatal period. In addition, those conditions for which no known prevention or treatment is or was available at the time of the birth have been included here. Examples include

- Late onset of abnormal neurologic behavior following a completely uneventful pregnancy, labor, delivery and neonatal course;
- Congenital anomalies;
- Unavoidable, noninduced prematurity (less than 35 weeks) or extremely low birth weights in both average-size-for-gestational-age and small-size-for-gestational-age infants;
- Complicated pregnancies associated with difficult conceptions, early bleeding and multiple infections, often viral;
- Unexplained catastrophic events occurring during labor or delivery;
- Nonpreventable congenital (TORCH [*to*xoplasmosis, *r*ubella, *c*ytomegalovirus, *h*erpes]) or perinatal infections.

Indeterminate included those cases that contained insufficient information, multiple factors or conflicting reports that made it impossible to determine which events were associated with or responsible for the outcome. Examples include

- Events related to pregnancy, labor and delivery were unrelated to outcome, but no record or report of care from the neonatal intensive care unit was available;
- Multiple injuries claimed, but examination at age 3 or 4 years showed no significant abnormalities;
- Poor pregnancy history, complicated delivery, multiple congenital anomalies and an intrapartum maternal death;
- Conflicts among the delivery record, the nursery record and the intensive care records relating to critical events during labor, delivery, Apgar scores, nursery course, and the like;
- Claims that certain equipment, staff, operating rooms or physicians were or were not available and in attendance at the time of delivery.

After all of the claims were classified, the frequency of each risk factor was compared between the preventable and nonpreventable groups to determine specificity, predictability and the relative risk of each factor.*

*We acknowledge the help of Ernest Scher, MD, and the epidemiologic advice and consultations of Leon Gordis, MD.

Statistical Analysis†

Frequency distributions of the risk factors were calculated for the entire study group. Of the 27 factors,‡ 20 occurred significantly more frequently than expected ($P \leq .05$, $\chi^2 = 3.841$) (Table 1). This was determined using a χ^2 test for a binomial proportion with one degree of freedom.[11(p194)]

The frequency of each of 25 risk factors‡ was then compared between the preventable and nonpreventable cases and the significance of the differences was determined using a 2×2 χ^2 analysis.[11] Once a significant difference ($P \leq .05$; $\chi^2 \geq 3.841$) in the occurrence of a risk factor was found, a case-control analysis was carried out and an odds ratio was calculated to estimate the relative risk of each factor or combinations of factors contributing to the outcome.[12(p426)]

Results

Profile of 'Brain Damage' Cases

The 250 records represented births from 1957 through 1982. Of 24 objective high risk factors‡ associated with poor pregnancy outcome, 20 were significantly increased in the study group (Table 1). Those with the highest risk ratios (2.8- to 16.0-fold) included maternal obesity (91 kg [200 lb] or more), diabetes, bleeding, twins, breech presentation, prematurity (less than 35 weeks' gestation), postmaturity (42 weeks or more), prolapsed cord, low one- and five-minute Apgar scores, birth weights 2.26 kg (5 lb) or less or more than 4.5 kg (10 lb). Neonates at risk were "floppy," had seizures and showed evidence of congenital infections and malformations. While no comparisons with frequencies in general populations were available, the number of mothers who had previous abortions (26%) and admissions for false labor (16%) and the number of infants transferred to neonatal intensive care units (45%) suggested these may be additional characteristics of this group.

It was not possible to do a multivariate analysis of the risk factors because one or more of the data items were either missing or not noted in a number of the records. This might induce a possible selection bias as well as question the validity of any medical conclusions derived from such an analysis.

Preventability

Of the 250 claims, 77 (31%) were classified as preventable and 105 (42%) as nonpreventable; 68 (27%) were indeterminate.

To evaluate preventability, the frequency distribu-

†Earl Diamond, PhD, provided statistical advice.

‡While 27 high risk factors were noted in a sufficient number of records to allow statistical comparisons, general population control data were available for only 24 of the 27 factors (see Table 1: "previous abortions," "admission for false labor" and "transfer to NICU"). Thus the discrepancy between 24 and 27. However, 20 factors occurred in significantly greater frequency in the study group.

When comparing the 27 "risk factors" between preventable and nonpreventable cases, it was necessary to delete three comparisons from Table 1 ("infertility," "diabetes" and "cord prolapse") because the total number in each group was too small. However, it was possible to compare the three factors from Table 1 noted above plus the concept of the late onset of neurologic deficiencies—thus allowing a statistical analysis of the 25 risk factors between preventable and nonpreventable "brain damage" cases.

tions and relative risks of 25 of the risk factors were compared between the preventable and nonpreventable cases. Odds ratios for preventability were calculated for each factor (Table 2). Only 13 factors differed significantly between the two groups and showed the highest odds ratios. These included prolonged gestation (42 weeks or more), cesarean birth, meconium staining, use of mid or high forceps, persistently low Apgar scores, high birth weight (4.5 kg or more), poor muscle tone and seizures. Only 4 of these 13 high-risk characteristics could be determined before birth and thus be amenable to intervention in the preventable group. In addition, the high frequency of all of these risk factors and the subsequent transfer of such infants to hospitals with neonatal intensive care facilities offer another approach to prevention. All of the other high-risk factors in the preventable group occurred after birth or during the neonatal period. In these infants, the specificity of the diagnosis is critical to be sure that the events recorded were or were not, in fact, due entirely to preventable causes.

In contrast, the only factors significantly associated with the nonpreventable group were congenital malformations, congenital infections and the late onset of neurologic abnormalities. The last group of factors were often found after what appeared to be a completely uneventful pregnancy, labor and delivery, yet were attributed to "perinatal asphyxia."

Discussion

A number of published retrospective studies[4,8] and at least one large prospective study[9] have correlated high-risk maternal, pregnancy and perinatal factors with neonatal neurologic damage. To our knowledge, however, no one has had the unique opportunity of reviewing a large number of claims of alleged "brain damage" in an attempt to establish cause. In addition to those preventable actions that could be attributed to family members or health care providers, the results of the present study strongly suggest that certain risk factors known to be associated with poor pregnancy outcome may be of value in discriminating between preventable and nonpreventable forms of neonatal "brain damage." These findings may be of value in resolving issues related to "brain damage" due to alleged negligence. It is clear from this review that some preventable events may be family induced and thus, defensible.

The methodologic problems in any retrospective analysis of medical records are well known. Considerable variability exists among the records of 250 infants born between 1957 and 1982 in community and university teaching hospitals in five states. However, the detailed information recorded by the insurance claims investigators provides a degree of uniformity. Furthermore, it would appear valid to compare the characteristics of the preventable and nonpreventable cases, because each risk factor was compared statistically only after all of the data had been recorded and the classification determined.

The occurrence of specific risk factors in each group has implications for preventive care. Some modifications in obstetric, neonatal and pediatric care appear warranted. The large number of indeterminate cases and the amount of information unavailable suggest the basic need for more complete medical and hospital records, the use of specific diagnostic techniques and clear identification of the causes of both preventable and nonpreventable alleged "brain damage."

Those risk factors and events that permit intervention and may reduce both the frequency of neonatal brain damage and liability litigation include the following:

1. Prolonged gestation (more than 42 weeks), which may be associated with an increase in neonatal morbidity and mortality,[3,8,13(p263),14] can be avoided by precise dating of the last menstrual period, when possible, and the use of ultrasound, stress tests and tests of fetal maturity[4] to determine the optimal time of delivery.

2. Mid or high forceps were used twice as often in preventable as in nonpreventable cases (22% versus

TABLE 2.—*Preventable and Nonpreventable "Brain Damage" Cases: Frequencies of Risk Factors and Their Relative Risks*

	Preventable 77 Cases (percent)	*Nonpreventable 105 Cases (percent)*	*Relative Risk**
Maternal			
Age ≥30 yr	27	23	1.27
Weight ≥91 kg (200 lb)	13	12	1.05
Gravida 1	43	36	1.32
Gravida 3 or more	26	26	1.01
Previous abortion	27	25	1.14
Current pregnancy, labor and delivery			
Bleeding	8	15	0.47
Twins	9	7	1.40
Breech	10	17	0.56
Admission for false labor	19	12	1.71
Gestation			
≤35 wk	14	22	0.59
≥42 wk	30	13	2.76†
Mid or high forceps	22	11	2.20†
Cesarean section	44	26	2.28†
Meconium	39	15	3.55†‡
Neonatal course			
Male sex	60	54	1.26
Apgar score, <5			
1 min	74	48	3.03†
5 min	57	29	3.24†
Birth weight			
≤2.26 kg (5 lb)	19	28	0.6
≥4.5 kg (10 lb)	17	4	5.24†‡
Poor tone, "floppy"	36	22	2.04†§
Seizures	51	26	2.96†§
Congenital infection	9	22	0.35†
Congenital malformation	4	32	0.08†
Transfer to NICU	52	32	2.25†
Late onset	1.3	27	0.04†

NICU = neonatal intensive care unit

*Odds ratio in case-control analyses.
†$P \leq .05$ by 2×2 χ^2.
‡Relative risk combining ≥4.5 kg plus meconium is 6.8.
§Relative risk combining poor tone plus seizures is 3.84.

11%), suggesting that the indications for their use should be precisely defined and limited to experienced physicians.

3. Cesarean delivery, which has been recommended to prevent damaged infants,[2,4] was either an emergency or a "crash" procedure in 97% of the preventable cases, often the result of failed use of mid or high forceps or of family pressure (20%) to have a "natural delivery." Early discussions with the family and consultations with colleagues before or early in labor may avoid undue delays.

4. Transfers of more than 50% of the neonates in the preventable group to a neonatal intensive care unit suggest that careful evaluation of a mother's risk factors and assessment of a hospital's capabilities be done before or early in labor.

5. Family pressures that prevent or interfere with sound medical practice require early detailed discussions with all concerned parties and with colleague consultants and proper notation of such in the medical records.

6. Inadequate diagnostic criteria in a neonate include the failure to carefully chart meconium staining —an important time-related event in labor[15]—head-chest circumferences, organomegaly and other stigmata of congenital infections or malformations.

7. "Birth asphyxia" or "perinatal anoxia" may be the only diagnosis in the absence of evidence of a careful workup to consider alternative causes. This should include a review of the maternal medical history and pregnancy record, the use of ultrasound, TORCH titers, immunoglobulin M values, cultures and other diagnostic criteria to establish an etiologic diagnosis that may be related to congenital or familial factors. These conditions may be associated with a higher frequency of abnormal labors and deliveries than in normal infants.[7,8]

8. The "late onset" of neurologic abnormalities, which occur months after the neonatal period (Table 2), has often been attributed to either "birth injury" or "perinatal anoxia" without evidence of carefully reviewing all of the records of the pregnancy, labor and delivery relating to preventable events at birth.[16] A complete family and genetic history and a thorough investigation of such postneonatal events as infections or trauma appear indicated before a final diagnosis.

Thus, both prenatal and postnatal events may be implicated in the increasing number of alleged neonatal "brain damage" claims. Preventable and nonpreventable causes require precise, recorded documentation in order to institute measures to reduce the frequency of neurologic damage and unwarranted claims.

While clearly recognizing the limitations of a retrospective study, the records reviewed, the data recorded and analyzed and the implications of the results strongly support the concept of additional studies of this type. Finally, a structured, detailed record that includes a family history, a genetic history and specific details related to a mother's prior medical history, previous and current pregnancies, labor and deliveries is recommended for all hospitals and should be used in assessing any claim of neonatal "brain damage" attributed to alleged negligence.

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'Baby Doe' Rulings—Review and Comment

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The recent controversy over the "Baby Doe" regulations issued by the Department of Health and Human Services represents the culmination of a dilemma that has faced the medical and legal professions for more than a decade. Although they have not been upheld by the courts, the regulations express the position that withholding treatment from defective newborns may constitute discrimination on the basis of handicap and advocate mechanisms for the reporting of such practices. Legislation regarding this issue is pending at both the national and state levels. The rulings have been disputed by many medical and professional groups, which are working to provide acceptable alternatives.

(Britton JR: 'Baby Doe' rulings—Review and comment [Medicine and Government]. West J Med 1984 Feb; 140:303-307.)

About 3% of all infants born in the United States have major birth defects.[1] Many of these defects are potentially life-threatening, while others may pose severe impediments to a normal existence. Recently, national attention has been focused on the dilemma of withholding treatment from defective newborns by regulations of the Department of Health and Human Services that have come to be known as "Baby Doe" rulings. Because these rulings could have a major effect on physicians caring for infants, their genesis and related legislation at both the state and national levels shall be reviewed.

Historical Perspectives

Although the frequency with which passive euthanasia for infants with birth defects has been practiced remains uncertain, surveys in the past two decades reported that as many as three out of four physicians exercised or condoned such a practice.[2,3(p399)] During the 1970s, decisions to withhold treatment from defective newborns gained increased attention in the medical literature. For example, Lorber proposed a series of criteria to determine the prognosis for quality of life among infants with meningomyelocele, suggesting that these criteria form the base for selecting those infants most likely to benefit from treatment; he advocated withholding therapy from the rest.[4] Similarly, Duff and Campbell in 1973 reported the practice of withholding treatment from handicapped infants when the prognosis, even with optimum treatment, was extremely poor; of 299 deaths in their nursery, 43 were the result of decisions not to treat.[5] This report generated a widespread debate in medical, legal, ethical and religious circles, and was followed by a hearing before the US Senate Committee on Health in 1974. Medical professional groups remained relatively silent, however, until the 1981 Judicial Council of the American Medical Association listed its general recommendations:

> In the making of decisions for the treatment of seriously deformed newborns or persons who are severely deteriorated victims of injury, illness, or advanced age, quality of life is a factor to be considered in determining what is best for the individual.
>
> In caring for defective infants the advice and judgment of the physician should be readily available, but the decision as to whether to treat a severely defective infant and exert maximal efforts to sustain life should be the choice of the parents. The parents should be told the options, expected benefits, risks, and limits of any proposed care; how the potential for human relationship is affected by the infant's condition; and relevant information and answers to their questions.[6(p8)]

A number of court decisions rendered in the 1970s highlighted the difficult and sometimes arbitrary nature of decisions to withhold treatment. In 1972 parents of a newborn with Down's syndrome born at Johns Hopkins Hospital refused consent for surgical correction of an intestinal atresia; a court order sought by physicians to operate was denied and the infant died of starvation.[3] In 1974 an infant with multiple anomalies was denied corrective surgical repair for a tracheoesophageal fistula by parents. Physicians caring for the baby filed a neglect petition, resulting in a court-ordered operation.[7] In 1979 parents refused to allow surgical correction of their infant's low-lying meningomyelocele; a hospital

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administrator petitioned the court to be appointed the infant's guardian in an effort to consent to the procedure and the court granted the petition.[8]

A number of writers cautioned that the potential legal implications of decisions to withhold treatment were vast, and concluded that civil and criminal liability could be incurred under numerous statutes including those for murder, child abuse and neglect.[3(p402),9] Indeed, a case occurred in Leicester, England, in 1980 in which parents of a newborn with Down's syndrome in respiratory distress reportedly chose not to have the infant survive, and this was written in the hospital chart. The infant was given a sedative and feedings were withheld, after which the child died. A member of a group called "Life" notified the police and murder charges were subsequently filed against the physician. After a lengthy trial, the physician was acquitted.[10]

The issue was perhaps brought into most dramatic focus by the now-famous Danville, Illinois, case in May of 1981 in which conjoined twins were born to a physician and his wife.[11] The infants were joined below the waist and shared the viscera of the lower portion of the body, including much of the gastrointestinal tract. A note written by a nurse and cosigned by the attending physician was placed on the chart of the infants stating "do not feed in accordance with parents' wishes." Contrary to expectations, the infants did not die, and nurses began to feed them. Eventually an anonymous caller notified the Illinois Department of Children and Family Services and a social service investigation followed. This culminated in a court order giving the state temporary custody of the twins, and charges including those of attempted murder were filed against both parents and attending physician. After substantial litigation the charges were dismissed because, as the ruling judge stated, it could not be proved that the statement in the chart was in fact a manifestation of the wishes of the parents and the attending physician.

As Sheila Taub of the University of Bridgeport (Conn) School of Law has stated, "The Danville case indicated that both law and medicine have been remiss in failing to develop mechanisms for dealing with a situation which occurs with some frequency."[11(p4)] These cases represented the first and currently only attempts to impose criminal liability for decisions to withhold treatment from defective newborns.

Recent National Developments

The recent Baby Doe rulings were prompted by a case bearing some similarity to the one occurring at Johns Hopkins in 1972: in April 1983 a 6-day-old infant with Down's syndrome subsequently referred to as "Baby Doe" died in Bloomington, Indiana, after a local court approved the parents' refusal to consent to surgical correction of esophageal atresia.[12] On April 30 the Secretary of Health and Human Services was directed to invoke laws prohibiting discrimination against the handicapped in future cases. Subsequently, the US Department of Health and Human Services (DHHS) ruled that it was unlawful to discriminatorily withhold feeding or medical care from a handicapped newborn.[13] This regulation was based on section 504 of the Rehabilitation Act of 1973, which provides that "No otherwise qualified handicapped individual . . . shall, solely by reason of his handicap, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving federal financial assistance."[13(p9631)] Section 504 also states that health services must be provided "on a basis of equality with those not handicapped." The new regulation required that hospitals receiving federal funding post notices in prominent places in delivery rooms, nurseries and maternity and pediatric wards, stating that "Discriminatory failure to feed or care for handicapped infants in this facility is prohibited by Federal Law." Special 24-hour hotline numbers were to be posted that could be used by anonymous informers to report failure to provide care or feeding to such infants. After announcement of this ruling, the American Academy of Pediatrics, the National Association of Children's Hospitals and related institutions and Children's Hospital Medical Center in Washington, DC, filed a joint suit against the United States Government, and on April 14, 1983, Federal District Judge Gerhard Gesell overturned the regulation, labeling it "arbitrary, capricious, and invalid," in that the record on which it was based did not support the imposition of the rule.[14] Judge Gesell further noted the absence from the record of any evaluation of potentially disruptive effects of the ruling on medical care, and commented that the regulation would "eliminate the role of the infant's parents in choosing an appropriate course of medical treatment."

The DHHS issued a revised proposal on July 5, 1983, that differs from the original one in that nondiscriminatory notices were smaller and to be posted only in nursing stations; moreover, the revised proposal included an appendix stating that "If a particular form of treatment is of dubious medical benefit to the patient or if the patient could not long survive even with the treatment, reasonable medical judgment could withhold the treatment."[15(p30852)] The appendix of the latest statement gives examples of alleged situations in which "denials of treatment . . . constitute a violation of section 504" of the Rehabilitation Act. These include denial of surgical correction of intestinal obstruction in Down's syndrome, denial of treatment for medically correctable physical anomalies in children born with spina bifida and denial of care on "grounds that a particular infant is potentially mentally impaired, or blind, or deaf, or lacking limbs."

Judge Gesell's overturning of the initial DHHS ruling was based largely on failure to satisfy a requirement of the Administrative Procedure Act in that it was promulgated without affording the public an opportunity to comment on the regulation before its publication in final form.[14] The second proposal allowed a 60-day comment period. The American Academy of Pediatrics has stated that this rule is little more than a carbon copy of the one struck down by Judge Gesell and is attempt-

ing to negotiate with the DHHS before issuance of a final regulation.[16]

Although the most recent DHHS statement is only a proposal, the "Infant Doe hotline" still exists. Moreover, the government may still choose to pursue investigations in accordance with its interpretation of section 504 of the Rehabilitation Act, as shown by its recent attempt to intervene in the case of "Baby Jane Doe," a newborn in New York with meningomyelocele and hydrocephalus whose parents decided to forego surgical intervention for the infant's problems ("Review and Outlook: Big Brother Doe," *The Wall Street Journal,* October 31, 1983, p 24). A series of court cases, initiated by an attorney who filed suit to reverse the parents' decision, led to a ruling by the New York State Court of Appeals in favor of the parents; this decision was sustained by the US Supreme Court on December 12, 1983 ("High Court Won't Hear Infant Case," *American Medical News,* December 23, 1983, p 1). However, the Justice Department had contended that the infant may have been discriminated against because of her handicap and requested a review of the medical records in the case. On November 17, US District Judge Leonard Wexler rejected these contentions ("Parents of 'Baby Jane Doe' Win in Court," *Tucson Citizen,* November 18, 1983, p 32), and the federal government is currently in the process of appealing.

It is ironic that the first DHHS ruling became effective one day after the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research issued a report addressing the same issue.[17] The Commission recommended the use of internal mechanisms—such as hospital ethics committees—to review cases in which parents and physician agree to withhold therapy in addition to those situations in which disagreement between these parties exists with respect to such questions. The Commission recommended that a handicapped infant should be given life-sustaining therapy in all cases when continued existence is likely to benefit the infant, irrespective of the impact on others. As the Commission stated, "This is a very strict standard in that it excludes consideration of the negative effects of an impaired child's life on other persons, including parents, siblings, and society." The American Academy of Pediatrics has endorsed the Commission's recommendations, suggesting that ethics committees be established on a trial basis in selected sites to provide for public comment and evaluation.[18]

In addition, bills are currently pending before both the Senate and the House of Representatives that relate to the Baby Doe issue. Both bills are proposed revisions of the Child Abuse Prevention and Treatment Act and the Child Abuse Prevention and Treatment and Adoption Reform Act of 1978. The House bill (HR 1904 of the 98th Congress) gives the states the discretion to act so as "to insure that nutrition (including fluid maintenance), medically indicated treatment, general care, and appropriate social services are provided to infants at risk with life-threatening congenital impairments" and to establish "a procedure for any interested person to report to appropriate authorities any known or suspected instance of the denial" of such measures. The bill further stipulates that state procedures should be consistent with guidelines set by DHHS "in consultation with providers of health care to infants at risk with life-threatening congenital impairments and their advocates . . . ." Notably, the House bill would require the Secretary of DHHS to review the report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research before setting procedural guidelines for the states. A study to determine the most effective means to provide federal financial support for the care of such infants is also required.

In the Senate, SB 1003 (of the 98th Congress) advocates the formation of a multidisciplinary advisory board that would include representatives of the handicapped and that would conduct a study of "local decision-making procedures involving the management of seriously ill newborns" and "make recommendations concerning appropriate procedural mechanisms to be utilized by health care facilities." Based on these recommendations, the Secretary of the DHHS would be required to set regulations for the establishment of local decision-making procedures. Failure by a hospital to comply with such regulations would result in loss of federal financial assistance. Moreover, the Senate bill would require "that all seriously ill newborns be provided relief from suffering including feeding, and medication for pain and sedation as appropriate."

Although the two bills propose different mechanisms, they share a common denominator in that the ultimate authority for the establishment of guidelines would reside with the Department of Health and Human Services.

Legislation at the State Level: Arizona as an Example

Concomitant with national developments, legislation has been enacted in two states, Arizona and Louisiana, regarding the Baby Doe issue. On April 27, 1983, Arizona's House bill 2209 was signed by the governor, and it is to go into delayed effect on July 1, 1984. Because this bill is the more recent and is similar to the earlier legislation in Louisiana (La RS 40:1299), it will be discussed in detail.

The Arizona bill (Arizona revised statutes 13-3620, 36-2281, 36-2282, 36-2283) is in part an amendment to the state's child abuse-reporting statute and provides that "A person shall not deny or deprive a newborn child of food, nutrients, water or oxygen with the intent to cause or allow the death of the child for any reason," including the presence of a "handicap which, in the opinion of the parent or parents of the child, the physician or another person, diminishes the quality of the child's life." The bill also provides that "A person shall not deprive a minor child of necessary life saving medical treatment or surgical care," although it does specify that this should not be construed to prevent a parent

from refusing consent to medical or surgical treatment that is not necessary to save the child's life or which has possible risks that outweigh possible benefits. Health care facilities with perinatal, obstetric or pediatric units must inform their employees of their duty to report any denial or deprivation of care or nourishment "with the intent to cause or allow the death of the child." Such reports must be made in the same manner as those for child abuse, and failure to do so is a class 2 misdemeanor, which carries a possible four-month prison sentence.

Neither a handicap nor the nature and extent of "necessary life-saving medical treatment or surgical care" are well defined in the Arizona bill. If the US House of Representatives bill (HR 1904) becomes law, the Arizona legislation could be sustained because the federal bill gives the states the discretion to act on these issues provided that state procedures remain consistent with future guidelines to be set by the Secretary of DHHS. Meanwhile, the Arizona Medical Association is lobbying to repeal the current state legislation.

Comment

Innumerable questions of both a legal and an ethical nature are raised by these recent government rulings, but their final resolution appears neither imminent nor simple. Further executive regulations, legislation and litigation will likely ensue, perhaps at both the national and state levels. If current rulings are upheld, the cost to society could be enormous. For example, in the immediate newborn period alone, many defective infants require intensive care, the average cost of which has been estimated at $8,000 per infant.[19(p19)] Although the potential economic impact of Baby Doe rulings has not been assessed, the personal financial burden to parents of long-term home care for chronic problems and frequent physician visits and hospital admissions for acute problems to which many such infants are prone may be great. Many families, realizing the extreme financial and emotional burdens involved in home care, may choose if possible to relinquish their infants to an agency or institution. In many states such facilities are often full and standards of care are low.[20] Moreover, because intensive care is required for many defective newborns, increasing the number of such infants will likely necessitate expansion of both physical facilities and nursing and physician staff in neonatal intensive care nurseries. Such expansion of health care supply to meet an increase in demand is likely to occur slowly, if at all, and in the interim other infants requiring intensive care may either be denied admission to an intensive care unit or receive compromised care by overextended staff. The institution of Baby Doe regulations could precipitate a health care shortage of crisis proportions, compromising both the quality and quantity of that care.

Under the current DHHS proposal, reports received on the "Infant Doe hotline" may lead to investigation of alleged denials of treatment. The details of two recent investigations by the DHHS "Special Assignment Baby Doe Squad" were recently presented in a special report in the *New England Journal of Medicine* by Dr James Strain, President of the American Academy of Pediatrics.[21] That such investigations may be detrimental to the well-being of infants and their families is suggested. As Dr Strain notes with respect to one case at Strong Memorial Hospital, Rochester, NY:

> In addition to the trauma caused by the birth of infants with profound congenital malformations, the parents were forced to deal with the investigation itself and with numerous local newspaper accounts of it. Parents of other critically ill children in the facility questioned the hospital administration on the adequacy of the care provided at Strong Memorial. On April 1, on the basis of newspaper reports and the belief that the facility was intentionally harming children, one family removed a seriously ill child from the hospital before his treatment had been completed.[21(p444)]

What role, if any, should legislative or executive rulings play in the Baby Doe issue? One legal writer, TS Ellis III, has recommended legislative determination of those conditions for which treatment is to be given or withheld, based on expert testimony from pertinent medical specialists.[3(pp418-423)] This alternative would be more specific and less confusing than the current Baby Doe rulings, and might be effective in clear-cut conditions. However, considering the number, complexity and variability of possible birth defects, it is unlikely that legislation on each would be a practical undertaking. In the final analysis, it is difficult to deny that most if not all decisions regarding the treatment of defective newborns must be made on an individual basis. Quality of life considerations, desires and concerns of the parents and economic implications for the family and society must all be weighed in the decision-making process. To routinely involve the courts in each case would be highly impractical. Among the more promising alternatives might be the use of hospital ethics committees similar to those suggested by Fost and others,[22,23] which could function in a manner analogous to institutional review boards for research on human subjects.[24] As mentioned, such committees have been recommended by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and the American Academy of Pediatrics. Indeed, an estimated 20% of hospitals in the United States have formal review mechanisms of some nature, although there is considerable debate among medical groups regarding the desirable composition and functioning of review committees. ("Medical Groups Divided on 'Baby Doe' Alternative," *American Medical News,* September 16, 1983, p 1). The American Academy of Pediatrics is currently considering the establishment of a task force to formulate guidelines for the organization and operation of such groups.

The recent Baby Doe rulings represent the culmination of a dilemma that has plagued the medical and legal professions for more than a decade. That decade has been punctuated by conflict and judging from current controversy, an end to this conflict does not seem to lie in the near future. Physicians should study

the issues and voice their opinions now before the final decision on the Baby Doe issue is made.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Sublingual Challenge Technique for the Diagnosis of Food Allergy

QUESTION:

Is it accepted medical practice to perform diagnostic evaluation of food allergy by the sublingual challenge technique?

OPINION:

In the opinion of the Scientific Advisory Panels on Allergy and Otolaryngology/Head and Neck Surgery, the sublingual challenge technique is unproved for the diagnosis of food allergy. There are no defined acceptable criteria for this procedure and its use has not been scientifically established.

Controlled double-blind studies have shown that the test results are not reproducible and indicate that the method is no better than tests with placebo.

Medical Schools of the West

Charles R. Drew Postgraduate Medical School

M. ALFRED HAYNES, MD, *Los Angeles*

The Drew Postgraduate Medical School is one of the newest institutions of medical education in the United States and so unusual that it is frequently misunderstood. The idea of building a postgraduate medical school was a direct consequence of the civil disturbances that occurred in Watts in 1965. The McCone Commission, which investigated the riots, included John McCone (former head of the Central Intelligence Agency) as Chairman, Warren Christopher (later Deputy Secretary of State and in charge of the Iranian hostage negotiations) as Vice Chairman and Dean Sherman Mellinkoff of UCLA. Among the recommendations of the Commission was to build a hospital for the area, which Los Angeles County implemented in 1972. This hospital, later to be known as the Martin Luther King, Jr, General Hospital, was envisioned from the very beginning to be a teaching hospital—associated with a postgraduate medical school that would train specialists in medicine and would provide continuing education for practitioners serving the area. The idea was that combining treatment and teaching would have an immediate impact on the quantity and quality of health care provided in the Watts-Willowbrook area. The Drew Medical Society, the local chapter of the National Medical Association, cosponsored the idea and the school was named, as was the society, in honor of a distinguished black surgeon—Dr Charles Drew.

The School's mission was defined early in its history: "To conduct medical education and medical research in the context of service to a defined population and to train persons to provide care with competence and compassion to this and other underserved populations." Because of its origins, the medical school has always had a strong orientation toward minority communities and underserved populations; this orientation is not incompatible with the pursuit of excellence. Like other medical schools, its main activities are service, education and research (Figures 1 and 2).

Service

Because medical education and medical research at Drew are based on service to the community, it is appropriate to discuss service first. Both hospital-based and community-based services are part of the program. The hospital provides general medical care at the 400-bed Martin Luther King, Jr, General Hospital and inpatient psychiatric services at the Augustus Hawkins Mental Health Unit. A major service provided at the hospital is the treatment of 60,000 cases of trauma each year in the Emergency Room, but other services are also heavily used. There are approximately 6,000 births each year at the hospital. The patient population is largely black and Hispanic, but there is a heterogeneous mix of other ethnic groups including white, American Indian and Samoan. The median age of the patients is younger than in the general population, and their health problems are often at a more advanced stage when they come to hospital than in the general population. Illnesses do not differ in kind, but they tend to differ in severity.

More than 20 community programs are conducted by the medical school. One of the largest is a Head Start Program that trains close to 1,000 children. This is one of several child development programs conducted by the Department of Pediatrics. These community programs also serve as a basis for education and research. For example, by seeing children in the hospital and in the community programs, a pediatrician is exposed to the entire spectrum of pediatric care that includes healthy children, physically handicapped chil-

(Haynes MA: Charles R. Drew Postgraduate Medical School [Medical Schools of the West]. West J Med 1984 Feb; 140:308-310.)

Dr Haynes is President and Dean of Charles R. Drew Postgraduate Medical School.
Reprint requests to M. Alfred Haynes, MD, King/Drew Medical Center, 1621 East 120th Street, Los Angeles, CA 90059.

Figure 1.—King/Drew Medical Center, a 400-bed teaching hospital serving the Watts-Willowbrook area of Los Angeles County.

Figure 2.—Another view of King/Drew Medical Center.

dren, abused children and children who are critically ill and under intensive care.

Education

Drew offers a wide range of educational opportunities in response to community needs. The core educational programs are in postgraduate and undergraduate medical education. The medical center trains about 250 residents and fellows in all the major specialties of medicine and has 24 medical students a year in the recently established Drew-UCLA undergraduate program. Early in its history, the school decided to provide opportunities for those who could not enter medicine, and there are a variety of allied health programs for training physician's assistants, radiographers, nuclear medicine and ultrasonography technicians and medical technologists. Plans are currently under way to integrate these programs under a single School of Allied Health Professions. To assure a continuous stream of young people who are prepared to enter health careers, a magnet high school was started on campus in 1983, and the Drew Area Health Education Center (AHEC), a component of the California AHEC system, is very active in developing opportunities in health careers. The Drew AHEC Program and the minority biomedical research programs attract young people from the surrounding area into various health and scientific careers.

Research

Although Drew's research activities are still in the developing stages, the School has conducted a sickle cell center for several years. The Fanon Center for Research and Development is one of the few national centers conducting behavioral research in special problems of minorities. Other major research interests include clinical and laboratory work in such areas as infectious disease and gastrointestinal ulcers, as well as in biomedical research. There is also institutional interest in research on violence. We at Drew expect significant expansion of research activities during the next decade and new research facilities are now being constructed.

Organization and Linkages

The School is organized into 11 major departments and almost all programs are under the auspices of a department chair. The chief executive officer is the President/Dean, who reports to the Board of Directors. There are two vice presidents, an academic vice president and a vice president for finance and administration. The associate and assistant deans are responsible for specific areas such as faculty affairs, student affairs and research. The arrangement of department chairs and deans constitutes a matrix form of organization.

The most important of the School's linkages with other institutions is that with the University of California. The linkage with the hospital forms the King-Drew Medical Center. The medical faculty of the

School are employees of the county and the medical school and they are compensated from both sources. The 150 regular, full-time faculty are expected to meet obligations in the hospital and in the School.

Under the terms of the 1978 Affiliation Agreement, a majority of the faculty must hold in-residence appointments at the University of California, Los Angeles (UCLA), so the faculty must meet the standards of both Drew School and the University of California.

The Undergraduate Medical Education Program is a joint program accredited by the Liaison Committee on Medical Education and its operation also fulfills UCLA's accreditation requirements. The Drew School could not exist at the present time without the important and very supportive linkages that have been formed with the county and the university.

Support

The Charles R. Drew Postgraduate Medical School shows what can be accomplished when there is good will and a desire to do something positive. It began with a grant from the federal Regional Medical Programs and is one of the most important survivors of that project. The symbiotic relationship with the County of Los Angeles makes support of the faculty possible and, in turn, the School attracts staff of a caliber that Los Angeles County might not otherwise find in its applicant pool. The State of California makes a significant contribution to the School in two ways. Recognizing the public service contributions of the School, Senator Mervyn Dymally introduced legislation, which was subsequently signed by then-Governor Reagan, that authorized appropriation of funds for some of the public service programs the School performs under contract with the University of California. Later, when the joint Drew-UCLA program began, this program was partially funded by the State of California through the University of California. The medical school is also supported by federal grants and contracts.

Because of its financial assistance from county, state and federal governments, the School is sometimes considered a public school. Actually, it is a fine example of a joint public-private venture. Drawing support and meaning from the local and national communities, it remains deeply responsive to local, state and national needs. It selects and trains persons in a very serious effort to meet the shortages in specialty and geographic distribution that characterize medical care, especially to the poor and minorities, in the state and in the nation. The emphasis on minorities and on primary care is, therefore, intentional.

Contributions

In the decade since the medical center became active, it has trained many physicians and allied health personnel, most of whom have committed themselves to serving otherwise underserved populations. Drew School has created opportunities for leadership in the health field for many young persons who might not otherwise have had such an opportunity. For example, it trains the largest concentration of minorities in the field of anesthesiology. It has one of the few programs that attract a significant number of minorities in ophthalmology and in otolaryngology. It has a very active program in emergency medicine. With Charles Drew as a role model, it continues to have a strong commitment to excellence.

The Future

Drew School has six goals: to achieve academic excellence and to deliver high quality patient care; to make original contributions in the field of medicine, especially for underserved populations; to continue its fiscal and administrative strength and growth; to influence the health care system, and to promote unity within the medical center. These goals can be achieved in time. Although the economic climate at present is such that even to survive is an accomplishment, this climate will not last forever and we expect to do more than just survive.

Information

Radial Keratotomy

A Controversial Issue in Ophthalmology

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IT HAS BEEN five years since the first radial keratotomy operation was performed in the United States. These years have been marked with heated debate and controversy regarding the safety and efficacy of this operation. This debate has spawned research on both animals and humans and many clinical series have been reported. The National Eye Institute-funded "Prospective Evaluation of Radial Keratotomy" (PERK) is also under way to determine the statistical probabilities of the safety and efficacy of this operation.

There is good evidence that eight incisions placed radially in the cornea from a predefined central zone to the corneoscleral limbus will produce central flattening of the cornea. This can be done safely in most cases. What is in doubt is the predictability of the operation. This lack of predictability is the major drawback of radial keratotomy today. Interestingly, the lack of predictability is present in the early reported clinical series and in the more recent series in which newer instrumentation and techniques have been used.

In 1981 Bores and co-workers[1] reported the results of radial keratotomy in 400 eyes of 223 patients with myopia ranging from −2 to −11 diopters, and with less than 1½ diopters of astigmatism. A surgical procedure was carried out using a #76A Beaver blade and with 16 radiating incisions extending from a premarked central optical zone to the limbus. The depth of the incision was then 75%. The results of this series showed an average postoperative refraction of −3.12 diopters in the first 97 cases and −1.18 diopters in the next 303 cases. The change in refractive error, however, was not tabulated in this study, nor was the change in keratometry readings. The reported postoperative sequelae included persistent epithelial defects, stromal edema, fluctuating visual acuity, glare and an endothelial cell loss of 6.3%.

Rowsey and Balyeat[2] evaluated the results of radial keratotomy done in 126 eyes of 102 patients. The patients were all older than 18 years of age and had stable myopia between −2 and −14 diopters. They evaluated various optical zones ranging from 3 mm to 5 mm and with radial incisions numbering from 4 to 16. Incisions were made with a 45-degree Superblade set at 90% of the corneal thickness. In Rowsey's report, the change in keratometry ranges from 2.45 to 4.12 diopters. In all, 32% of the patients had uncorrected visual acuity of 20/20 or better, 24% had visual acuity ranging from 20/25 to 20/40 and 43% had 20/50 visual acuity or worse. Early complications of this series included perforation, persistent epithelial defects and stromal edema; late complications included fluctuating visual acuity in 48% of patients, glare in 74%, endothelial cell loss in 6.9% and overcorrection in 4% to 14% of the patients.

More recently, Arrowsmith and colleagues[3] have reported their experience with radial keratotomy done by the Fyodorov technique. They prospectively evaluated radial keratotomy done in 156 eyes of 101 patients using the Fyodorov formulas. At six months postoperatively, 43% of the patients had 20/20 visual acuity, 73% had better than 20/40 visual acuity and 51% of the eyes were within 1 diopter of emmetropia. If patients who had less than 6 diopters of myopia were considered, the results were even better. Unfortunately, these results are reported as means and unless the standard error is considered, these numbers may be misleading. For instance, the mean spherical equivalent refractive error at six months was −0.2 diopters in 156 eyes; the standard deviation of this mean, however, was 2.4 diopters and the range was −9.5 diopters to +8.4 diopters. Stated in this statistical fashion, the authors can ensure an individual patient of a 95% chance of having a visual acuity rather than a spherical equivalent dioptric refractive error from −4.6 diopters to +4.6 diopters.

The reasons for the lack of predictability are not obvious. Although there are problems with quantifying and ensuring consistency of depth of incision and length of incision between operations, there are probably numerous factors that play a role in the ultimate visual acuity achieved. Even using the nomograms of Fyodorov, which take into account scleral rigidity, intraocular pressure and many other parameters, the surgical results lack the predictability desired for an operation that is done on eyes that have correctable visual acuity of 20/20 with spectacles or contact lenses.

The long-term effects of radial keratotomy are not yet known. Endothelial cell loss from the procedure does not appear at present to be a major concern; however, only long-term follow-up will ensure that the damage to the endothelium is not significant. Each physician must decide whether the risks of the surgical procedure overcome the potential improvement in visual acuity and life-style for patients.

(Schanzlin DJ: Radial keratotomy—A controversial issue in ophthalmology [Information]. West J Med 1984 Feb; 140: 311.)

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

A PRIMER OF ORTHOPAEDIC BIOMECHANICS—George Van B. Cochran, MD, MScD, Director, Orthopaedic Engineering and Research Center, Helen Hayes Hospital, West Haverstraw, NY; Professor of Clinical Orthopaedic Surgery, College of Physicians and Surgeons, Columbia University, New York. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 413 pages, $48.00.

The cascade of engineering technology relevant to orthopedics makes this first edition text of Dr Cochran's unusually timely. Medical education including orthopedic resident training is generally deficient in the important subject matter presented. The orderly simplicity with which Dr Cochran has covered the large field of biomechanics makes his book easy reading and understandable. He has overcome the "terminology barrier" and "math anxiety" so frequently encountered by surgeons attempting to understand the fundamental physical information relevant to human stance and movement.

The relatively new field of biomechanical and rehabilitation engineering is attracting students from a wide variety of disciplines including mechanical, electrical, chemical and materials engineering. Currently, orthopedics involves human body interfacing with a great many inert materials. These vary from external prosthetic and orthotic devices to a numerous and sometimes confusing number of implanted products replacing joints, stabilizing fractures and generally improving function, relieving pain and providing cosmesis.

Dr Cochran is highly qualified to write the material presented in this book. It was a delight to read. The book should be included as required reading for orthopedists and engineers involved in biological technology. It is sufficiently basic and informative that its inclusion in required reading for medical students should be considered. Physical therapists, prosthetists, orthotists, occupational therapists, and other allied health personnel involved in rehabilitation of patients with mobility deficits will also find the material informative and challenging.

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* * *

SNAKE VENOM POISONING—Findlay E. Russell, MD, PhD, Professor of Pharmacology and Toxicology, University of Arizona, Tucson; Adjunct Professor of Neurology, University of Southern California, Los Angeles; and Adjunct Professor of Neuro-pharmacology, Loma Linda University, Loma Linda, California. Scholium International, Inc., 265 Great Neck Rd., Great Neck, NY 11021, 1983. 562 pages, $57.50.

The author, Dr Findlay Russell, is an internationally recognized authority on animal toxins and human envenomation. His book represents the culmination of a lifetime of work with over 25 years of clinical and research experience in this specialized field. The result is the definitive and up-to-date textbook on venomous snakes and their disastrous encounters with man. Dr Russell writes not only from extensive personal experience but with an intimate knowledge of the world's literature. His library contains every published book concerning biology of snakes, pharmacology and chemistry of their venom, and the effects of their bites, as well as collected reprints from the literature of the world's journals—many in foreign languages. Fortunately for the reader, Dr Russell has evaluated this mass of literature for accuracy and for significance.

The writing in such comprehensive texts often tends to be dull and trite. However, this book may be read for pleasure as well as profit. Dr Russell's book is a delight to peruse, whether or not one ever encounters a snake-bitten patient. Dr Russell does not hesitate to add the personal touch—he is not afraid to use the pronoun "I" or to boldly state his personal opinion. There are flashes of humor throughout the text. Rarely does one encounter a scholarly book so enjoyable to read.

While the book was written with practicing physicians in mind, it includes the basic knowledge of snake biology essential to better patient care. The subject matter covers the structure and behavior of both North American and exotic foreign snakes (which one may encounter in treating proprietors of "underground zoos"), the composition and pharmacology of venoms, the medical treatment of snakebite (with a caution about the surgical treatment) and myths and folklore that surround these misunderstood reptiles. As an encore, Dr Russell covers the problems of envenomation by the dreaded lizards of the southwest, Gila monsters and beaded lizards.

The publishers have produced a book with large clear type, profusely illustrated with Dr Russell's photographs and line drawings. The cover is certain to catch one's eye on any bookshelf. This book is easy to read even by a weary clinician after a hard day's work.

Only approximately 7,000 snakebites will reach the medical profession each year. Consequently, practitioners often are uncertain about the therapy for this emergency in their panic-stricken patients. Dr Russell's tome, therefore, should be in the library of every hospital that offers emergency services. It should be required reading for all emergency room physicians and is highly recommended for all practitioners in areas in which venomous snakes abound—particularly, the south and southwest. Since snakebites involve many disciplines (immunology, pathology, chemistry and pharmacology), the book should be a welcome and authoritative addition to these libraries. Finally, even a physician practicing in the heart of a large city might enjoy reading this book. Who knows when a physician may be called upon to treat a patient who has just been bitten by a "pet" cobra?

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CARDIOVASCULAR PATHOLOGY—Volumes I and II—Edited by Malcolm D. Silver, MD, PhD, FRCPA, FRCP(C), Professor and Chairman, Department of Pathology, Health Sciences Centre, University of Western Ontario Faculty of Medicine, and Chief of Pathology, University Hospital, London, Ontario. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 1,407 pages, $190.00.

This is a two-volume treatise on cardiac pathology edited by M. D. Silver and written by a distinguished international panel of pathologists with special interest in cardiovascular diseases. There are 37 chapters which cover not only the standard subjects but several pathological aspects of present-day cardiac technology (cardiac pacing, coronary bypass grafts). Throughout the text, great weight is given to clinical considerations and clinical-pathological correlations, which makes the book particularly valuable to clinical cardiologists.

Despite the multiplicity of authors, the book is well edited—chapters are clearly written with a minimum of overlap in related subjects. The print and illustrations are excellent and each chapter has a well-edited bibliography.

Certain chapters were of particular interest to this reviewer: "Age-related cardiovascular changes," "Disease of the coronary arteries," "Ischemic diseases of the myocardium," "Postoperative congenital cardiac disease." (The subject of congenital heart disease in general is not included in the book because of the feeling that good texts limited to this subject are available—which is the right decision.)

Some minor defects are noted: The chapter on the conducting system is disappointing—anatomic basis for arrhythmias is treated very briefly. The divisions of the left bundle branch and their diseases are dealt with in a brief paragraph.

In general this is a valuable addition to the libraries not only of pathologists but cardiologists and cardiovascular surgeons as well. Also, it would be a good reference book for students and house staff. It is highly recommended.

ARTHUR SELZER, MD
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* * *

STEROIDS IN ASTHMA: A REAPPRAISAL IN THE LIGHT OF INHALATION THERAPY—Edited by T. J. H. Clark, Professor of Thoracic Medicine, Guy's Hospital Medical School, London. John Wright/PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 233 pages, $42.50.

Most medical monographs carefully cultivate the facade of impartiality and objectivity. T. J. H. Clark, the editor of *Steroids in Asthma* plays no such charade. It is his personal "view [that] the baleful reputation of systemic corticosteroids has cast too long a shadow over the treatment of asthma inappropriately limiting the more widespread use of inhaled corticosteroids." He then selects monograph contributors who are, in essence, given the charge to support this view. The reader is immediately put on notice that this book may not be worthwhile. Next, the reader thumbs through the book which has the elegance that commercial artists impart to drug company advertising (big print, wide margins, multicolor figures, glossy photographs) but which is nearly devoid of standard deviations and contains no measures of statistical significance. Finally, the reader notes that 3 of the 12 contributors are from New Zealand. What do they know about asthma in New Zealand! Should the reader put down the book and move on? No.

The elegant format that makes the monograph suspicious, the panache of style common to English writers and the attention-getting topic headings in the left margins make this monograph a delight to read. More important, the book is worthwhile for its medical content. The editor has fairly warned the reader that this book is a polemic and the contributors provide lively and, for the most part, intelligent support of that polemic. The reader must remain cautious. Conclusions are drawn that may or may not be true. For instance, Compton in Chapter 11 states that pediatricians inexplicably use methylxanthines and implies that inhaled corticosteroids are preferable. I ask Dr Compton, "Where is the long-term study comparing methylxanthines with inhaled steroids?"

Steroids in Asthma is a genre of monographs that is all too rare. It is not only a book about medical facts but about medical style. It conveys the experiences, insights, opinions and clinical techniques of the contributors. Topics range from the epidemiology of asthma to a guide on how to correctly use inhalers. (The title of *Steroids in Asthma* is misleading since the monograph concerns a much broader approach to asthma.) The contributors are attuned to providing the reader with information useful in the practical management of asthmatic patients. Although I admonish the reader to be wary of the monograph's sweeping conclusions, the reader will have a better fund of information about asthma and have guidelines on how to interpret and use that information. Incidentally, I now know that New Zealand has a lot to teach me about asthma.

BERTRAND J. SHAPIRO, MD
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UCLA School of Medicine
Director, Respiratory Therapy Department
UCLA Medical Center
Los Angeles

* * *

ATLAS OF SURGICAL OPERATIONS, Fifth Edition—Robert M. Zollinger, MD, DSc(Hon), FACS, FRCS(Hon) England and Edinburgh, Emeritus Regents Professor and Chairman of the Department of Surgery, The Ohio State University College of Medicine, and Chief of the Surgical Service, University Hospitals, The Ohio State University, Columbus, Ohio; and Robert M. Zollinger, Jr, MD, FACS, Associate Professor of Surgery, Case Western Reserve University School of Medicine and University Hospitals, Cleveland, Ohio. Macmillan Publishing Co., Inc., 866 Third Ave., New York, NY 10022, 1983. 436 pages, $80.00.

My reaction to a detailed inspection of the Fifth Edition of the *Atlas of Surgical Operations* by Zollinger and Zollinger is the same as my reaction more than 40 years ago when I received a copy of the First Edition of this atlas by Elliott C. Cutler and Robert Zollinger: "How can any surgeon be without it?" Until the new Fifth Edition arrived I still found many occasions to refer to my first edition and later to Volume II published in 1967 for a presurgical review of the technical details of an operation, sometimes of an operation I had performed many times before and in some cases where minor details of my technique differed from those presented by the authors. However, I have always found their clear line drawings and brief pertinent comments to be helpful.

Volume II published in 1967 was designed to present the more complicated procedures and to complement the standard operations presented in Volume I. The Fifth Edition presents a combination of procedures of both categories with various additions and deletions of subjects from previous editions giving a final presentation of 206 chapters or sections.

Selection of procedures to be covered in a general atlas of this type of course is a major task and reflects the interests and the background of the authors. The first plate of the first edition was tonsillectomy, a procedure that has been deleted from later editions despite the fact that it is still one of the most commonly performed operative procedures in this country. The authors probably agree with many surgeons and most pediatricians that the procedure is greatly overused. The section on gynecological procedures is retained and there is an extensive section on vascular surgery.

In the thoracic surgery section the technique of pneumomectomy and lobectomy have been omitted but rib resection and thoracotomy incisions, which a general surgeon might use for certain elective and emergency procedures, are appropriately retained.

Considerable space is devoted to radical mastectomy although it is stated that "radical mastectomy is no longer a routine procedure for carcinoma of the breast," and few such operations are being performed in most US hospitals today. Despite the strong public pressure to continue the evaluation of even less extensive excisional procedures than modified radical mastectomy there is no discussion of partial mastectomy.

This addition is an update of a format that has been highly successful for more than 40 years. The general selection of important procedures, the excellent clear artwork and the brief but pertinent text will continue to make this volume essential to the library of every student, practitioner and teacher of surgery.

WILLIAM P. LONGMIRE, Jr MD
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UCLA School of Medicine
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Veterans Administration
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* * *

CLINICAL MANAGEMENT OF POISONING AND DRUG OVERDOSE—Lester M. Haddad, MD, Clinical Assistant Professor, Medical College of Georgia; Director, Savannah Regional EMS Poison Center; Director of Education, Department of Emergency Medicine, Memorial Medical Center, Savannah, Georgia; and James F. Winchester, MD, FRCP, Associate Professor of Medicine, Georgetown University School of Medicine, and Co-Director of Hemodialysis, Hemoperfusion and Transplantation Services, Georgetown University Medical Center, Washington, DC. W B Saunders Company, West Washington Square, Philadelphia, PA 19105, 1983. 1,012 pages, $75.00.

Haddad and Winchester have collaborated with 84 authors to prepare 107 chapters in a new text of 1,000 pages concerning the management of poisoning and drug overdose. In the past five years there has been an explosion of new data in the field of clinical toxicology. This text is conveniently divided into two parts: the first part deals with a general approach to poisoning and the second concerns specific agents. This division

helps to set a solid base on which to interpret more complicated presentations.

The editors have done an admirable job in keeping the text readable. The tables are remarkably uniform with frequent subtitles and good indexing. There are relatively up-to-date bibliographies. Especially interesting are unique chapters such as "Management of Chemical and Drug Injury to the Eye," "Environmental Toxins," "Marine Toxicology," "Nonsteroidal Antiinflammatory Agents and Colchicine Overdose," "Complications of Cytotoxic and Immunosuppressive Chemotherapy," "Effects of Toxins on Gastrointestinal Tract," "Methyl Bromide and Related Compounds" and even "Tear Gas and Other Riot Control Agents."

As with any text with such a broad scope, there is some unevenness. The early chapters may be too elementary. The pictures of snakes, mushrooms, fish and plants are generally too small to be of clinical use. The major concern is that this up-to-date text will require frequent updating as new information becomes available. Nonetheless this easy-to-read text is a must for emergency physicians. It will be especially useful as an adjunct to poison control centers and fills the need for a solid textbook in a rapidly evolving area. There is something for everyone in this text.

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Occupational Health Center
San Francisco General Hospital Medical Center
San Francisco

* * *

ANNUAL REVIEW OF IMMUNOLOGY—VOLUME I—Edited by William E. Paul, National Institutes of Health, Bethesda, Maryland. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA 94306, 1983. 655 pages, $27.00 (USA), $30.00 (elsewhere).

This book is the first volume in a new series—*The Annual Review of Immunology*—and is the 25th in the series of annual review volumes. This volume, as the other annual reviews, is not for the "faint of heart." There are 22 chapters, each by separate authors and each an in-depth review and critique of a major area in the rapidly expanding field of basic immunology. For the most part each chapter is an intense detailed evaluation of a major immunologic area of contribution. Furthermore, there are extensive references at the end of each chapter which will serve the most interested scientist as a good bibliography. These chapter-reviews will primarily be of interest to serious scientists, researchers or students and certainly will be beyond the level for most persons not working directly in the field or with particular expertise and interest in a particular area. The topics chosen for review seem a bit eclectic as they range across cellular interactions, complement receptors, structure and regulation of immunoglobulin genes, idiotypes, cell-mediated immunity to malaria and on and on. However, realizing the book is the first volume of the *Annual Review of Immunology* makes this quite understandable. There is such a wealth of material it is hard to know where to begin. Thus the *Annual Review of Immunology* certainly is an idea whose time has come and the editors should be complimented on getting out such an in-depth and up-to-date volume. Scientists and students of immunology now will be able to look forward to succinct critical reviews of important issues annually.

ANDREW SAXON, MD, *Chief*
Associate Professor of Medicine
Chief, Division of Clinical Immunology-Allergy
Department of Medicine
UCLA School of Medicine
Los Angeles

* * *

GENERAL OPHTHALMOLOGY—10th Edition—Daniel Vaughan, MD, Clinical Professor of Ophthalmology, University of California, San Francisco, and Taylor Asbury, MD, Clinical Professor of Ophthalmology, College of Medicine, University of Cincinnati. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 389 pages, $17.00 (softbound).

This profusely and helpfully illustrated volume is a mainstay of medical student education. In this, the latest in a series of editions beginning in 1958, the book has grown to 407 pages. As such, it borders on being too extensive for medical student consumption, yet such is the progress of medicine in all of its specialties.

General Ophthalmology is factual and concise. It places emphasis in the appropriate areas for the medical student or general physician. The division into logical chapters, and the excellent index add to its usefulness, particularly in view of the fact that it is now a substantial book.

The book is easy to read. It has extensive, up-to-date references at the conclusion of each chapter. Relatively newer areas of ophthalmology, such as immunology and genetic disorders, are appropriately represented by their own chapters.

There is no better current reference in ophthalmology for the medical student and general physician.

ROBERT S. HEPLER, MD
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* * *

VASCULAR GRAFTING—CLINICAL APPLICATIONS AND TECHNIQUES—Edited by Creighton B. Wright, MD, Clinical Professor of Surgery, Uniformed Services University of the Health Sciences, and Professor of Clinical Surgery, University of Cincinnati, Cincinnati. John Wright/PSG Inc, 545 Great Road, Littleton, MA 01460, 1983. 386 pages, $54.00.

This excellent volume contains probably the most complete discussion of vascular grafts in one place that has been published to date. Although for the average surgeon it may be "more than I wanted to know about penguins," for the vascular surgeon it is most certainly a basic text that contains encyclopedic information and references on what are in reality the basic tools of the profession.

The history of vascular grafting is traced, with significant developments annotated along the way. The development, fabrication and characteristics of different graft materials are adequately reviewed in the separate chapters and the applicability, patency rates and biological characteristics of all current graft materials are extensively analyzed.

Of particular note is the discussion of PTFE grafts by Jack Cannon, an excellent review of femoropopliteal grafting by Thomas Lynch and Robert Hobson and a very comprehensive discussion of the autogenous saphenous vein graft by L. Paul Bosher. An excellent chapter on thrombosis by George J. Collins, Jr, reviews some basic hemotologic and coagulation concepts and places them in the perspective of host-graft interaction.

The book is well organized and with few exceptions reads very easily with good literary style, excellent editing and adequate references. Illustrations are sparse but, nevertheless, where found they are of good quality and helpful. With the notable exception of chapters by Lester Sauvage and Herbert Dardik, there is perhaps too little material on the actual technical facets of graft implantation. A more detailed discussion of graft implantation techniques, particularly indicating the specific technical differences between different graft materials, would be useful.

Another area not extensively covered in the text is management of specific graft complications such as sepsis, false aneurysm, graft disruption and seroma. It probably would be useful in a comprehensive discussion of vascular grafts to include a section on types and materials of sutures to be used in graft implantation.

On balance, however, this is an excellent basic reference text on vascular grafts with chapters written by clinicians and investigators at the forefront of graft development having wide experience in graft implantation.

This certainly would be a valuable addition to the library of any surgeon specializing in the practice of vascular surgery.

HERBERT I. MACHLEDER, MD
Professor of Surgery
Department of Surgery
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UCLA Center for the Health Sciences
Los Angeles

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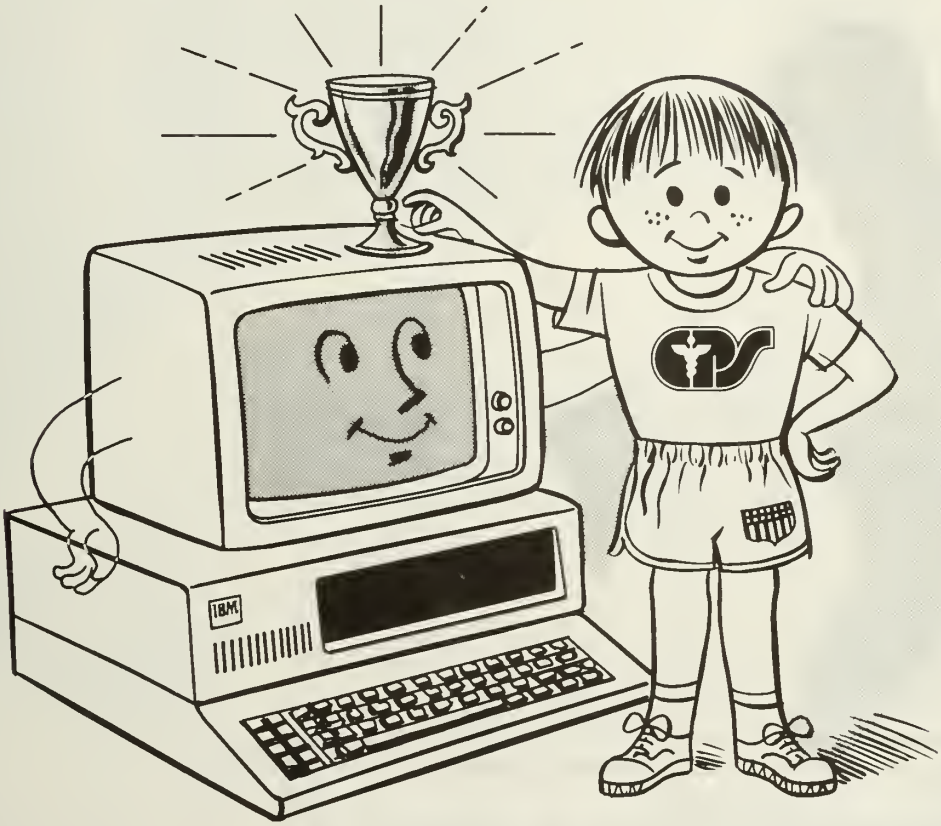

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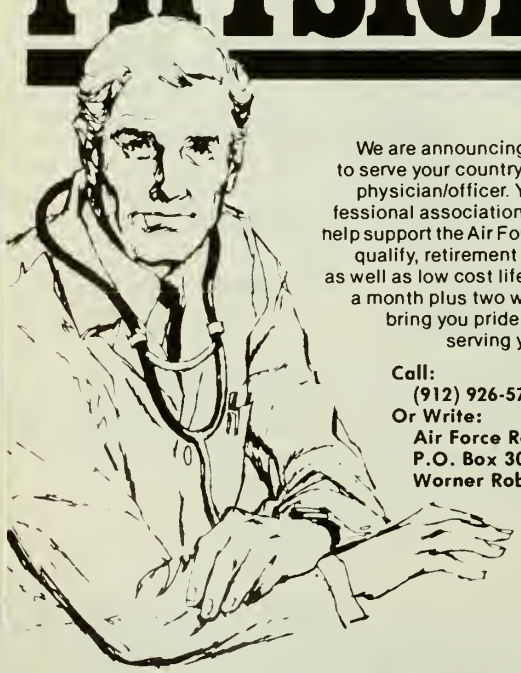

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(Continued on Page 320)

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(Continued from Page 318)

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Indications and Usage—LO OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception
Contraindications—OC's should not be used in women with any of the following conditions 1 Thrombophlebitis or thromboembolic disorders 2 A past history of deep-vein thrombophlebitis or thromboembolic disorders
3 Cerebral-vascular or coronary-artery disease
4 Known or suspected carcinoma of the breast
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding 7 Known or suspected pregnancy (see Warning No 5) 8 Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products
Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.
The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established Three principal studies in Great Britain and 3 in the U S have demonstrated increased risk of fatal and nontatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause
CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2 0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9 5 times greater in users than in nonusers.
MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not OC's, however, were found to be a clear additional risk factor In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke Furthermore, amount of smoking is also an important factor In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent
RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved This finding has been confirmed in the U S
ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs intermittent use Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception Estimates of risk of death for each method include combined risk of contraceptive method (e g , thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure This latter risk varies with effectiveness of method The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke Lowest mortality is associated with condom or diaphragm backed up by early abortion Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e g , thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately
A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users
If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.
2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.
3 *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's Of cases found in women without predisposing risk factors (e g irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC These are no longer marketed No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's Several studies have found no increase in breast cancer in women taking OC's or estrogens One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease Reduced occurrence of benign breast tumors in users of OC's has been well documented In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's Close clinical surveillance of all women on OC's is, nevertheless, essential In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's
4 *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage This has been reported in short-term as well as long-term users Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known
5 *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare This risk has been estimated to be of the order of 1 in 1,000 exposures or less Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy Male children so exposed may develop abnormalities of the urogenital tract Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy One case-control study estimated a 4 7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some exposures involved only a few days Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's Embryos with these anomalies are virtually always aborted spontaneously Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive Many clinicians recommend 3 months, although no precise information is available on which to base this The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy
6 *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use In one of the other studies, increased risk was apparent between 6 and 12 months' use
7 *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's For this reason, prediabetic and diabetic patients should be carefully observed while on OC's Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined
8 *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's In some women, hypertension may occur within a few months of beginning OC's In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year Age is also strongly correlated with development of hypertension in OC users
Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug
9 *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause
10 *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy If pathology has been excluded, time or change to another OC may solve the problem Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase risk of thromboembolic disease Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities
11 *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures
12 *Breast-feeding*—OC's given in the postpartum period may intertere with lactation and decrease quantity and quality of breast milk Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects, if any, on the breast-fed child have not been determined If feasible, defer OC's until infant has been weaned
Precautions—GENERAL—1 A complete medical and family history should be taken prior to initiation of OC's Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests As a general rule OC's should not be prescribed for longer than 1 year without another physical examination
2 Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.
3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related
4 OC's may cause some degree of fluid retention They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency
5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's If jaundice develops, OC's should be discontinued
6 Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution
7 OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency Clinical significance is undetermined
8 Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency
9 The pathologist should be advised of OC therapy when relevant specimens are submitted
10 Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's
a Increased sulfobromophthalein retention b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability c Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered
d Decreased pregnanediol excretion e Reduced response to metyrapone test
Information for the Patient—See Patient Package Labeling
Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline
Carcinogenesis—See Warnings on carcinogenic potential of OC's
Pregnancy—Category X See Contraindications, Warnings
Nursing Mothers—See Warnings
Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings) thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies
There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed mesenteric thrombosis, neuro-ocular lesions, e g , retinal thrombosis and optic neuritis
The following adverse reactions have been reported in patients on OC's and are believed to be drug-related Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma which may persist, breast changes tenderness, enlargement, and secretion, change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic); mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses
The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria
Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children Overdosage may cause nausea, and withdrawal bleeding may occur in females

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(Continued from Page 214)

July 10-12—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday. 22 hrs. $300.

August 1-4—**Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday.

August 11-18—**4th Annual Fine Needle Aspiration.** UCSF. One week.

August 17-19—**Nutrition, Obesity, and Weight Control—White Water Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

IDAHO

February 18-25—**Up-to-Date Cardiac Therapy: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Sun Valley. 24 hrs. Contact: Richard F. Paris, MD, (208) 788-4995.

February 19-25—**Effective Management of Common Sports Injuries: An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

February 25-March 3—**Effective Diagnosis and Treatment of Infectious Diseases—An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

February 26-March 3—**Current Therapy for Dermatological Disease: An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

March 4-10—**New Considerations in Family Practice: A Review.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

March 25-April 1—**Procedures and Concepts in Ambulatory Gynecology: An EPIC Medical Expedition.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

April 1-7—**Establishing Precise Radiographic Diagnoses for Traumatic Injuries.** Sun Valley. 24 hrs. Sponsors and Contact: See above, February 18-25.

MONTANA

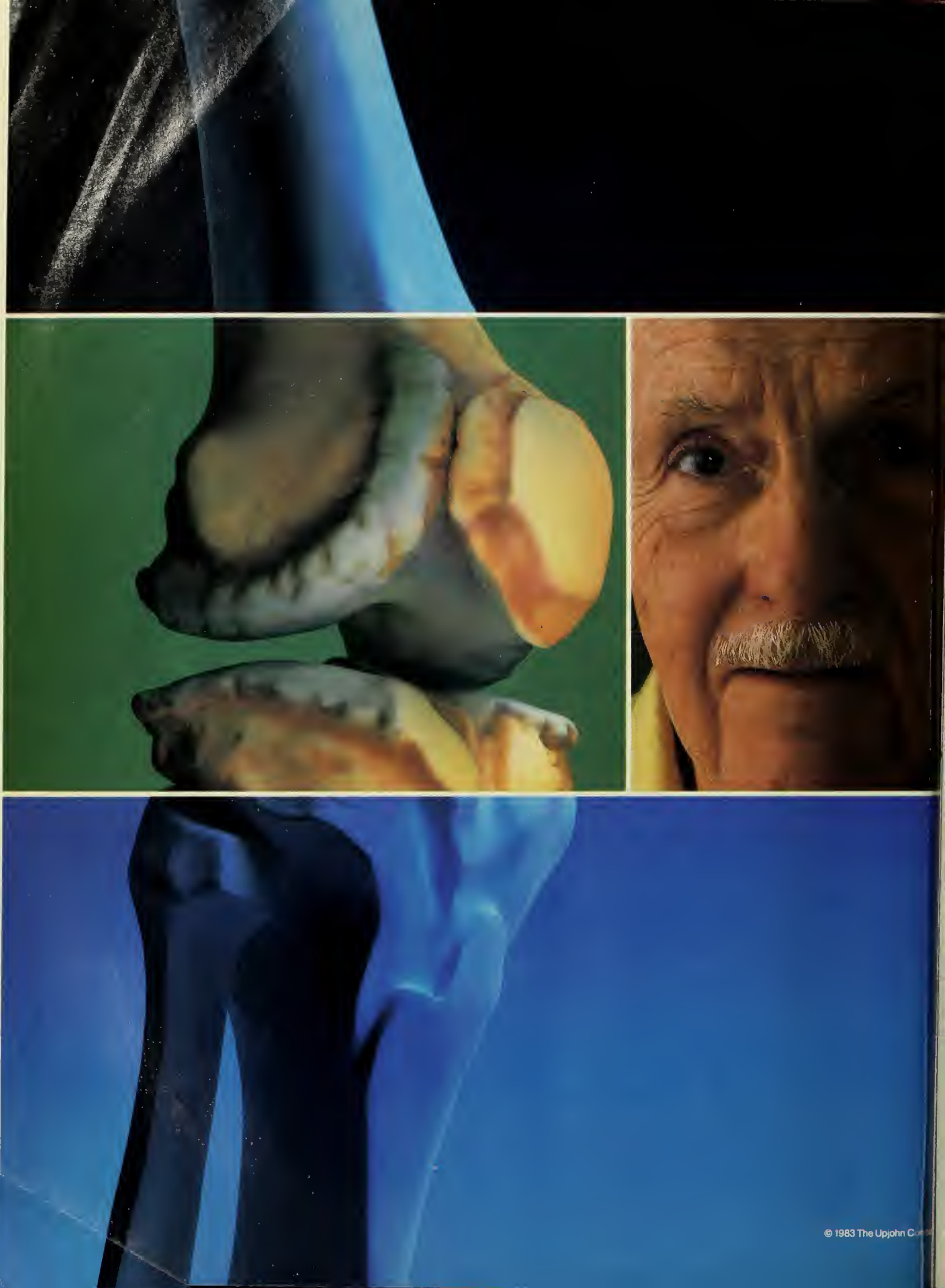
March 21-24—**Big Sky Lung Summit.** American Lung Assn. of Montana at Big Sky of Montana "Ski the Sky." Wednesday-Saturday. Contact: ALA of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite

(Continued on Page 326)



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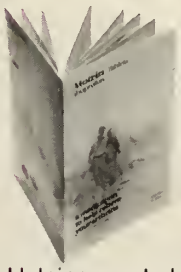
Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.



New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

Helping you to help your patients—
Ask your Upjohn Representative for a complimentary supply.

The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS
(ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.
Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.
Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.
The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.
Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.
Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.
Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.
Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness;* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence less than 1%—Probable Causal Relationship*
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence less than 1%—Causal Relationship Unknown*
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.
*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
Caution: Federal law prohibits dispensing without prescription.

Motrin is a registered trademark of The Upjohn Manufacturing Company M, Barceloneta, Puerto Rico

MED B-7-S

J-3255 September 1983

Upjohn

(Continued from Page 323)

204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 19-22—**Annual Meeting/South Central Association of Blood Banks.** Albuquerque. Sunday-Wednesday. Albuquerque Convention Center. 28 hrs. AMA Cat. I, NM Cat. IV. Contact: Toby L. Simon, MD, P.O. Box 25445, Albuquerque 87125. (505) 843-6227.

February 23-25—**17th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

February 24-26—**12th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 11 hrs. NM Cat. IV. Contact: David Lorber, MD, 1101 Medical Arts Ave., NE, No. 4, Albuquerque 87102. (505) 842-5105.

February 27-March 2—**Purgatory Ski Symposium at Tamarron.** Tamarron, Colorado. Monday-Friday. Tamarron Lodge. 20 hrs. AAFP Prescribed. Contact: Jack Greenberg, MD, Bernalillo County Chapter, AAFP, 2121 Juan Tabo NE, Albuquerque 87112. (505) 292-4500.

March 18-21—**Rural Health Care: Bringing It Home.** Albuquerque. Sunday-Wednesday. Convention Center. 19 hrs. AMA Cat. I, NM Cat. IV. Contact: Judy Harris, RN, New Mexico Health Resources, Inc., P.O. Box 8735, Albuquerque 87198.

May 3-4—**New Mexico Medical Society Annual Meeting.** Santa Fe. Thursday-Friday. Hilton Inn. 10 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Ste 204, Albuquerque 87108. (505) 266-7868.

May 24-25—**Chronic Pain: Current Status and Future Directions.** Santa Fe. Thursday-Friday. La Fonda Hotel. 10¼ hrs. NM Cat. IV. Contact: Ms Helene Slansky, Coordinator, Santa Fe Neurological Sciences Institute, St. Vincent Hospital, Box 5764, Santa Fe 87501. (505) 983-4744.

July 16-19—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, P.O. Box 23070, Albuquerque 87192. (505) 298-5300.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center. 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contac: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month. 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

FAMILY PRACTICE

February 13-17—**15th Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: OHSU-CME.

March 1-4—**Update in Rheumatology: Spring Ski at Mt. Bachelor.** Thursday-Sunday. Inn of the Seventh Mountain, Bend. Contact: OHSU-CME.

May 18-19—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion Motor Inn at Jantzen Beach. Contact: OHSU-CME.

SURGERY

March 2-3—**Difficult Problems in Surgery: Gastrointestinal Malignancies.** Portland. Friday-Saturday. Red Lion-Lloyd Center. Contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

March 8-9—**Occupational Medicine.** Portland. Thursday-Friday. Red Lion at Jantzen Beach. Contact: OHSU-CME.

March 29-30—**Health Problems in the Workplace.** Thursday-Friday. Portland. Red Lion-Lloyd Center. Contact: OHSU-CME.

March 29-31—**First Annual Mt. Bachelor Winter Sports and Mountaineering Medicine Conference.** Bend. Sponsor: Siskiyou General Hospital, Yreka, California. Thursday-Saturday. Inn of the Seventh Mountain. 18 hrs. $195, physicians; $170, nurses and physical therapists. Contact: Daniel A. Williams, Jr, MD, 746 S. Main, Yreka, CA 96097. (916) 842-4383.

April 12-13—**School of Medicine Alumni Scientific Sessions and Sommer Lectures.** Portland. Thursday-Friday. OHSU Campus. Contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the Ameri-

(Continued on Page 334)

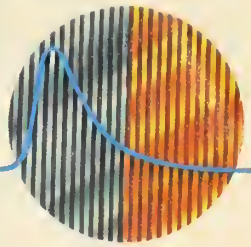
SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

Halcion® 0.25 mg Tablets

triazolam CIV

Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

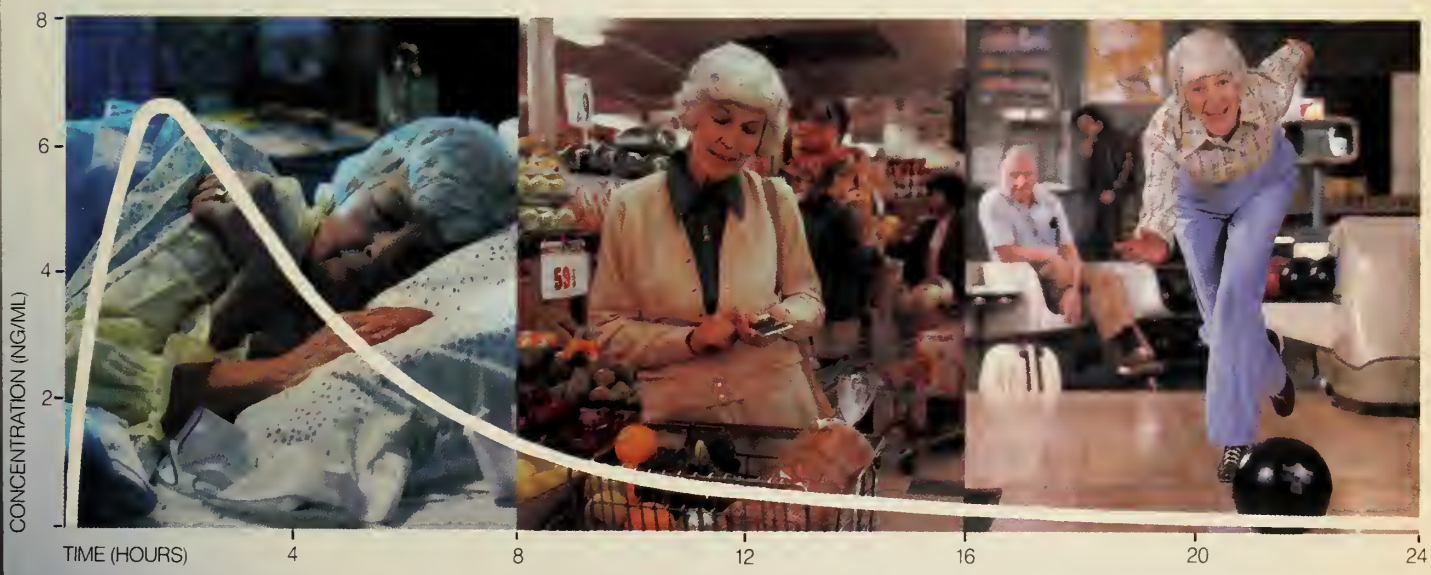
Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.



RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion

triazolam IV

0.25 mg Tablets
Initiate at 0.125 mg

© 1983 The Upjohn Company

Halcion Tablets
triazolam IV

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam IV

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

An added complication... in the treatment of bacterial bronchitis*

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary: Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor* (cefaclor, Lilly) is administered to a nursing woman

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbiliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.*

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

References

1. Antimicrob. Agents Chemother., *8*:91, 1975
2. Antimicrob. Agents Chemother., *11*:470, 1977
3. Antimicrob. Agents Chemother., *13*:584, 1978
4. Antimicrob. Agents Chemother., *12*:490, 1977
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob. Agents Chemother., *13*:861, 1978
7. Data on file, Eli Lilly and Company
8. Principles and Practice of Infectious Diseases (edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett), p. 487. New York: John Wiley & Sons, 1979

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

300035

Valium® (diazepam) CIV interacts with Inderal® (propranolol HCl)

Wyeth Laboratories
Philadelphia, PA 19101

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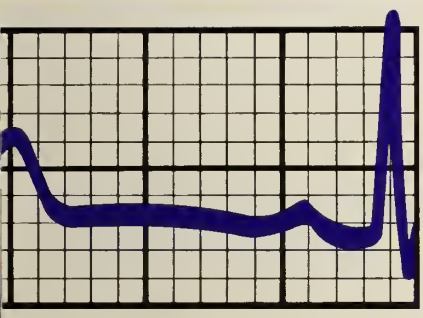
Ativan® (lorazepam) does not.



Inderal® (propranolol HCl) prolongs Valium elimination half-life

Inderal significantly impairs the clearance of Valium® (diazepam)®

But Inderal® has no significant effect on either the half-life or clearance of Ativan

Eight participants received single IV doses of diazepam (5-10 mg) and single IV doses of lorazepam (2 mg) in a drug-free control state and again with concomitant propranolol therapy (80 mg tid). Results of the concomitant use were as follows:

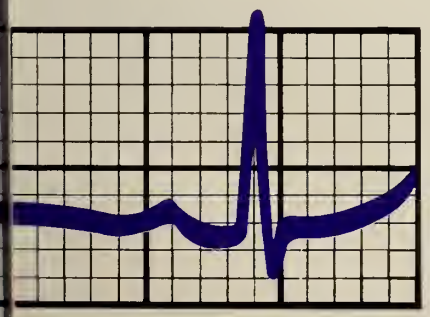
- ☐ Propranolol increased diazepam elimination half-life and significantly reduced diazepam clearance.[1]

This finding is consistent with previous reports of coadministration of Valium with cimetidine[2] and with oral contraceptives.[3]

- ☐ However, propranolol had no significant effect on Ativan volume of distribution, elimination half-life or total clearance.[1]

Although the clinical significance of the diazepam-propranolol interaction has not as yet been documented, such interaction may be worthy of consideration when prescribing for anxious patients on propranolol therapy.

Ativan® for (lorazepam)® Anxiety



References:
1. Ochs HR, Greenblatt DJ, Abernethy DR: In press.
2. Klotz U, Reimann I: N Engl J Med 302:1012-1014, 1980.
3. Abernethy DR, Greenblatt DJ, Divoll M, et al: N Engl J Med 306:791-792, 1982.

See important information on following page.

The appearance of these tablets is a registered trademark of Wyeth Laboratories

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

Wyeth Laboratories
Philadelphia, PA 19101

(Continued from Page 327)

can Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE GRAND ROUNDS

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Wednesday—8:00-9:00 a.m. Contact: Thomas Schwenk, MD, (801) 581-8633.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

February 17-21—**29th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. 16 hrs. Fee to be announced. Contact: K. C. Wong, MD, (801) 581-6115.

February 18-22—**25th Annual OB/GYN Update** (Sponsor: University of Utah). Saturday-Wednesday. Park City, 14½ hrs. Fee to be announced. Contact: James Scott, MD, (801) 581-5501.

February 22-25—**Gynecologic Oncology Update** (Sponsor: University of Utah). Wednesday-Saturday. Park City. 14½ hrs. Fee to be announced. Contact: James Scott, MD, (801) 581-5501.

February 27-March 2—**3rd Annual Park City Dermatology Seminar** (Sponsor: University of Utah). Monday-Thursday. Park City Yarrow (Holiday Inn). 18 hrs. Fee to be announced. Contact: Gerald Krueger, MD, (801) 581-7837.

February 29-March 3—**Nuclear Medicine Update** (Sponsor: University of Utah). Wednesday-Saturday. Park City Yarrow (Holiday Inn). 23 hrs. Fee to be announced. Contact: Andrew Taylor, MD, (801) 581-2716.

March 3-10—**Primary Care: Clinical Problems in Otolaryngology—Head and Neck Surgery** (Sponsor: University of California, San Francisco). One week. Park City. Contact: UCSF, Extended Programs in Medical Education, Room 569U, San Francisco 94143. (415) 666-4251.

March 5-9—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. 25 hrs. Fee to be announced. Contact: Jennifer Fossum, (801) 581-7803.

March 8-9—**Lasers in Urologic Surgery** (Sponsor: University of Utah). Thursday-Friday. Park City Yarrow (Holiday Inn). 11 hrs. Fee to be announced. Contact: Jay Smith, MD, (801) 581-7674.

March 9-10—**Primary Care of Hand Injuries** (Sponsor: University of Utah). Friday-Saturday. Park City Yarrow (Holiday Inn). 9½ hrs. Fee to be announced. Contact: Ronald Mann, MD, (801) 581-3713.

March 12-16—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. 24 hrs. Fee to be announced. Contact: Jennifer Fossum, (801) 581-3581.

March 12-16—**Introduction to Microcomputers for the Primary Care MD** (Sponsor: University of Utah). Monday-Friday. Park City Yarrow (Holiday Inn). 22½ hrs. Fee to be announced. Contact: Larry Lutz/Wayne Peay, (801) 581-8052.

March 16—**Annual Clinical Ophthalmology Meeting** (Sponsor: University of Utah). Friday. Salt Lake City. 6 hrs. Fee to be announced. Contact: Mano Swartz, MD, (801) 581-6384.

March 21-23—**Infection Control Update** (Sponsor: University of Utah). Wednesday-Friday. Salt Lake City. 15 hrs. Fee to be announced. Contact: Sego Matsumiya, RN, (801) 582-6384.

March 22-23—**6th Annual Conference on Medical Genetics** (Sponsor: University of Utah). Thursday-Friday. U of U campus. 14 hrs. Fee to be announced. Contact: John Carey, MD, (801) 581-8943.

March 26-30—**4th Annual Nutrition in Contemporary Medicine Conference** (Sponsor: University of Utah). Monday-Friday. Park City, Shadow Ridge Hotel. 29½ hrs. Fee to be announced. Contact: Jennifer Fossum, (801) 581-7803.

April 20—**Symposia in Infectious Disease** (Sponsor: University of Utah). Friday. Salt Lake City, Hotel Utah. Credit and fee to be announced. Contact: Zell McGee, MD, (801) 581-8201.

June 3-6—**American Society for Lasers in Medicine and Surgery** (Sponsor: University of Utah). Monday-Wednesday. Salt Lake City. 8 hrs. Fee to be announced. Contact: John Dixon, MD, (801) 581-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

February 16-17—**Winter Clinical Symposium.** Wenatchee. Thursday-Friday. Thunderbird Motor Inn. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

February 18—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

February 18-25—(IDAHO) **Sports Medicine.** Sun Valley. One week. Contact: U/W.

February 23-24—**Respiratory Protection.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

February 24-25—**Revolutions in Laboratory Medicine and Pathology: What Clinicians Need to Know.** Seattle. Friday-Saturday. Virginia Mason Hospital Auditorium. Contact: VMMC.

February 29—**Laboratory Diagnosis for Clinicians.** Seattle. Wednesday. Northwest Hospital. Contact: Charlotte Kennedy, Northwest Hospital, Education and Training Dept., 1550 N. 115th St., Seattle 98133. (206) 364-0500, ext. 1737.

March 1-2—**Hospital Infections 1984.** Seattle. Thursday-Friday. Contact: U/W.

March 2—**Occupational Neurological Diseases.** Seattle. Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

March 3-10—(HAWAII) **Diagnosis and Drug Therapy.** Saturday-Saturday. Sheraton Royal Waikoloa, Island of Hawaii. Contact: U/W.

March 8—**Diabetes: Latest Concepts in Treatment.** Seattle. Thursday. Ballard Community Hospital. Contact: U/W.

March 9-10—**Hematology and Oncology.** Seattle. Friday-Saturday. Museum of History and Industry. Contact: U/W.

March 9-10—**Focus, 1985: Critical Care.** Tacoma. Friday-Saturday. Tacoma Multicare Medical Center. Contact: Maxine Bailey, College of Medical Education, 705 S. 9th, #203, Tacoma 98405.

March 10-17—(HAWAII) **Financial Planning for Physicians.** Saturday-Saturday. Inter-Continental Hotel, Maui. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

March 14—**Medical Ethics.** Seattle. Wednesday. Northwest Hospital. Contact: Charlotte Kennedy, Northwest Hospital, Education and Training Dept., 1550 N. 115th St., Seattle 98133. (206) 364-0500, ext. 1737.

March 15-18—**45th Annual Meeting of the North Pacific Society of Neurology and Psychiatry.** Seattle. Thursday-Sunday. Contact: Mary Helen Pullen, Executive Secretary, Department of Neurology, Oregon Health Sciences University, Portland, OR 97201. (503) 225-7772.

March 17—**Office Laboratory Diagnosis for the Physician.** Seattle. U/W Health Sciences Center. Contact: U/W.

March 17-24—(HAWAII) **Obstetrics and Gynecology.** Saturday-Saturday. Waikiki Hyatt, Oahu. Contact: U/W.

March 18-25—(HAWAII). **The Spine.** Sunday-Sunday. Westin Wailea Beach, Maui. Contact: U/W.

March 21-23—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

March 22-23—**Advanced Cardiac Life Support.** Seattle. Thursday. U/W Health Sciences Center. Contact: U/W.

March 24—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

March 24-31—(HAWAII) **The Injured Patient: Controversies and Challenges.** Saturday-Saturday. Kauai Sheraton, Kauai. Contact: U/W.

March 29—**Pediatric Ophthalmology.** Seattle. Thursday. Children's Orthopedic Hospital. Contact: Patti Smith, Meeting Coordinator, Washington State Academy of Ophthalmology, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

March 31-April 7—(HAWAII) **High-Risk Infants and Adolescents.** Saturday-Saturday. Inter-Continental Hotel, Maui. Contact: U/W.

April 2-13—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Sheraton Hotel. Contact: U/W.

April 4-6—**Introduction to Industrial Hygiene.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

April 5-6—**Arrythmias.** Seattle. Thursday-Friday. U/W Health Sciences Center. Contact: U/W.

April 6—**John, Jane and Baby Doe: Bioethical Issues.** Seattle. Friday. Children's Orthopedic Hospital. Contact: U/W.

April 7—**Schizophrenia.** Seattle. Saturday. Madison Hotel. Contact: U/W.

April 12-14—**Chronic Disease in Office Practice.** Seattle. Thursday-Saturday. Seattle Sheraton. Contact: U/W.

April 13-14—**Patient Safety and Risk Management in Anesthesia.** Seattle. Friday-Saturday. Westin Hotel. Contact: Patti Smith, Executive Secretary, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

April 14—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

April 20-21—**Endocrine Day.** Union. Friday-Saturday. Alderbrook Inn. Contact: U/W.

April 26—**Travel and Medicine.** Seattle. Thursday. Park Hilton Hotel. Contact: U/W.

April 27-28—**Industrial Back Pain.** Seattle. Friday-Saturday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

(Continued on Page 338)

References:
1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
PROCARDIA* (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PRDCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PRDCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PRDCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PRDCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PRDCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PRDCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PRDCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. © 1982, Pfizer Inc.

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PFIZER INC

"I can do things that I couldn't do for 3 yrs. including joining the human race again."

Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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"My daily routine consisted of sitting in my chair trying to stay alive."

"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

for the varied faces of angina

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: June 8-12, 1984, Valdez Convention Center.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 27-28, 1984, Scottsdale Conference Center, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 10-15, 1984, Disneyland Hotel, Anaheim.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: 1984—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1984—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-28, 1984, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 3-6, 1984, Desert Inn, Las Vegas.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 2-4, 1984, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: April 27-29, 1984, Salizhan Lodge, Gleneden Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 24-28, 1984, Jackson Lake Lodge, Moran.

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May 3-4—**Health Issues for Exercising Women.** Seattle. Thursday-Friday. U/W Health Sciences Center. Contact: U/W.

May 5-6—**Advanced Cardiac Life Support.** Seattle. Saturday-Sunday. U/W Health Sciences Center. Contact: U/W.

May 11—**Adverse Drug Reactions in Surgery.** Seattle. Friday. Ballard Hospital. Contact: U/W.

May 12-13—**Pharmacology for Anesthesiologists.** Seattle. Saturday-Sunday. U/W Health Sciences Center. Contact: U/W.

May 16-18—**Noise Measurement and Control.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

May 17-18—**Prevention of Chronicity in Back Pain.** Seattle. Thursday-Friday. Seattle Sheraton. Contact: U/W.

May 18—**Basic Computer Understanding.** Seattle. Friday. Seattle Trade Center. Contact: U/W.

May 24-25—**Hereditary Diseases of the Nervous System.** Seattle. Thursday-Friday. Mayflower Park Plaza. Contact: U/W.

June 1-2—**Health Hazards in the Modern Office.** Seattle. Friday-Saturday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

June 9—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

June 14-15—**Use of Microcomputers in Occupational Safety and Health.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 12-13—**Second Annual Conference on Occupational Hazards to Health Care Workers.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 27-29—**Seafair VI Pediatric Anesthesia and Intensive Care.** Seattle. Friday-Sunday. Seattle Sheraton. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave, Suite 900, Seattle 98121. (206) 623-4801.

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Uniquely specific...Limbitrol is the only agent that treats anxious depression with amitriptyline and the specific anxiolytic action of Librium® (chlordiazepoxide HCl/Roche).

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Dramatic reduction of somatic symptoms...Early, middle and late insomnia associated with anxious depression dropped 91%, 87% and 89% respectively after only two weeks of Limbitrol therapy. GI complaints associated with anxious depression dropped 73% after two weeks, and headaches decreased 79% in two weeks, 88% in four weeks.[2]

Documented effect on mood
...including marked improvement in the first week with regard to psychic and somatic anxiety, guilt, anorexia and insomnia.[2]

Superior compliance...which can be seen as a result of the early and broad symptom relief of Limbitrol; insomnia (late and middle), agitation, psychic and somatic anxiety, hypochondriasis and feelings of worthlessness are usually reduced within the first week of therapy as measured on the Hamilton Depression Scale.[1]

***h.s.* dosage for most patients**...with flexible dosage schedules for all patients, including *t.i.d.* and combined *h.s.*/a.m. doses.

Low cardiotoxicity...Only 1.9% of the patients in two multicenter studies reported cardiovascular side effects.[2]

Few side effects and few dropouts...Only 4% of the Limbitrol patients dropped out of therapy because of side effects, while 13% of the amitriptyline patients dropped out.[1]

Patients should be cautioned about the combined effects of Limbitrol and alcohol and other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car.

References: 1. Feighner JP *et al: Psychopharmacology 61* 217-225, Mar 22, 1979
2. Data on file, Hoffmann-La Roche Inc., Nutley, NJ

In moderate depression and anxiety

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
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Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving)

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide)
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated. sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue
Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly
Limbitrol 10-25: initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5: initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50

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Because square pegs don't fit round holes

Please see summary of product information on reverse side.

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- Undiminished efficacy for at least 28 nights[2-4]
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Caution patients about driving, operating hazardous machinery or drinking alcohol during therapy. Limit dose to 15 mg in elderly or debilitated patients. Contraindicated during pregnancy.

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See next page for references and summary of product information.

References. 1. Kales J *et al: Clin Pharmacol Ther* 12:691-697, Jul-Aug 1971. 2. Kales A *et al: Clin Pharmacol Ther* 18:356-363, Sep 1975. 3. Kales A *et al: Clin Pharmacol Ther* 19:576-583, May 1976. 4. Kales A *et al: Clin Pharmacol Ther* 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc* 27:541-546, Dec 1979. 6. Kales A, Kales JD: *J Clin Pharmacol* 3:140-150, Apr 1983. 7. Montt JM: *Methods Find Exp Clin Pharmacol* 3:303-326, May 1981. 8. Greenblatt DJ *et al: Sleep* 5 (Suppl 1):S18-S27, 1982. 9. Kales A *et al: Pharmacology* 26:121-137, 1983. 10. Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther* 21:355-361, Mar 1977. 11. Zimmerman AM: *Curr Ther Res* 13:18-22, Jan 1971. 12. Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983.

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided, with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults*: 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients*: 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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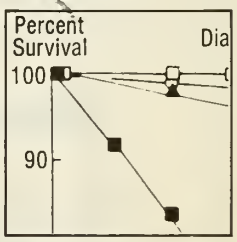

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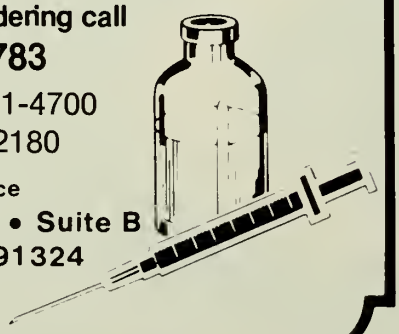

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Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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ACE*INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function*, Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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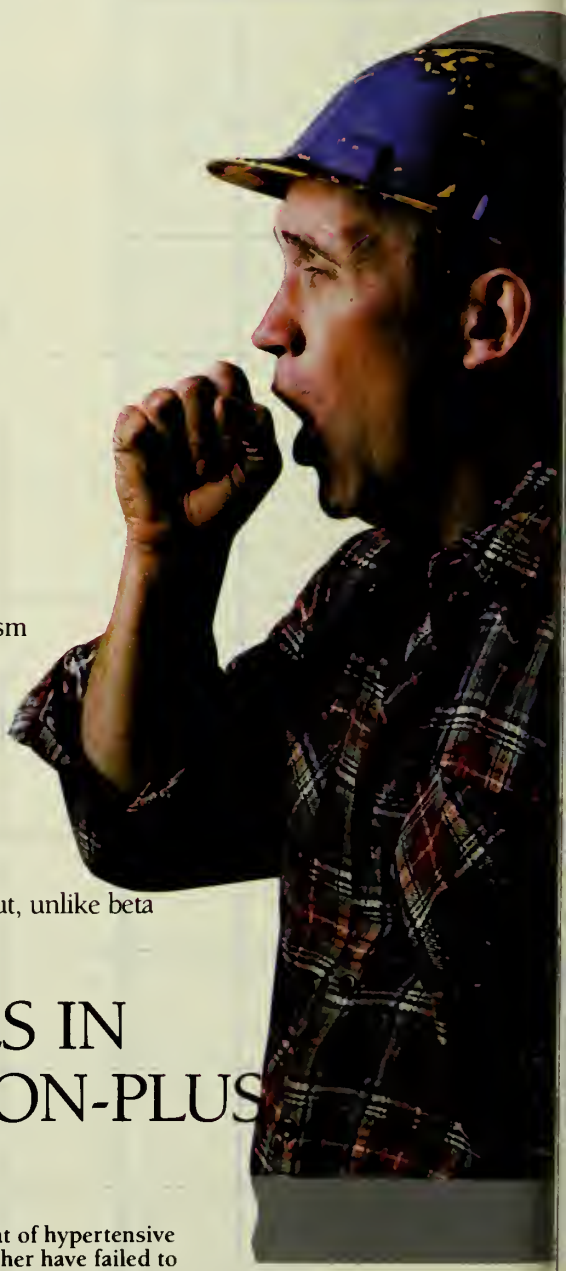

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CAPOTEN improves cardiac output, unlike beta blockers

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Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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Dr Miller is Director, Studies on Smoking, Edinboro, Pennsylvania.

636 Commentary: **What to Do Because Evidence Links Involuntary (Passive) Smoking With Lung Cancer**
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Dr Glantz is Associate Professor of Medicine, Division of Cardiology, Department of Medicine, and Member, Cardiovascular Research Institute, University of California, San Francisco.

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From the Division of Research and Socioeconomics, California Medical Association, San Francisco.

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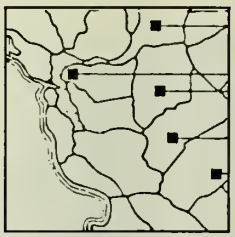
ROBERT C. DAVIDSON, MD, MPH, and JANE FOX
From the Department of Family Practice, University of California, Davis, School of Medicine.



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Dr Mann was State Epidemiologist, State of New Mexico Health and Environment Department, Santa Fe, at the time this article was submitted. He is now with the Centers for Disease Control.

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From the Departments of Community and Family Medicine and Medicine, University of California, San Diego, School of Medicine.

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★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

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In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

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Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456
2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*
4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*
6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Acknowledgments

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Before prescribing, consult the complete package circular.

Indications and Usage: Treatment of hypertension, alone or in combination with a thiazide diuretic

Contraindication: Known sensitivity to the drug

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INFORMATION FOR PATIENTS Advise patients on **Wytensin** to exercise caution when operating dangerous machinery or motor vehicles until it is determined they do not become drowsy or dizzy Warn patients that tolerance for alcohol and other CNS depressants may be diminished Advise patients not to discontinue therapy abruptly

LAB TESTS In clinical trials, no clinically significant lab test abnormalities were identified during acute or chronic therapy Tests included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test During long-term use there was small decrease in serum cholesterol and total triglycerides without change in high-density lipoprotein fraction In rare instances occasional nonprogressive increase in liver enzymes was observed, but no clinical evidence of hepatic disease

DRUG INTERACTIONS **Wytensin** was not demonstrated to cause drug interactions when given with other drugs, e g , digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials However, potential for increased sedation when given concomitantly with CNS depressants should be noted

DRUG/LAB TEST INTERACTIONS No lab test abnormalities were identified with **Wytensin** use

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY No evidence of carcinogenic potential emerged in rats during a two-year oral study with **Wytensin** at up to 9 5 mg/kg/day, i e , about 10 times maximum recommended human dose In the Salmonella microsome mutagenicity (Ames) test system, **Wytensin** at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture In another eukaryotic system, *Saccharomyces cerevisiae*, **Wytensin** produced no activity in an assay measuring induction of repairable DNA damage Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9 6 mg/kg), suggesting impairment of fertility Fertility of treated males (9 6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy

PREGNANCY Pregnancy Category C WYTENSIN® MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN A teratology study in mice indicated possible increase in skeletal abnormalities when **Wytensin** is given orally at doses 3 to 6 times maximum recommended human dose of 1 0 mg/kg These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits However, increased fetal loss has been observed after oral **Wytensin** given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg) Reproductive studies in rats have shown slightly decreased live-birth-indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6 4 and 9 6 mg/kg There are no adequate, well-controlled studies in pregnant women **Wytensin** should be used during pregnancy only if potential benefit justifies potential risk to fetus

NURSING MOTHERS Because no information is available on **Wytensin** excretion in human milk, it should not be given to nursing mothers

PEDIATRIC USE Safety and effectiveness in children less than 12 years of age have not been demonstrated, use in this age group cannot be recommended

Adverse Reactions: Incidence of adverse effects was ascertained from controlled clinical studies in U S and is based on data from 859 patients on **Wytensin** for up to 3 years There is some evidence that side effects are dose-related Following table shows incidence of adverse effects in at least 5% of patients in study comparing **Wytensin** to placebo, at starting dose of 8 mg b i d

Adverse Effect	Placebo (%) n = 102	**Wytensin** (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20% Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less Cardiovascular—chest pain, edema, arrhythmias, palpitations Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort Central nervous system—anxiety, ataxia, depression, sleep disturbances ENT disorders—nasal congestion Eye disorders—blurring of vision Musculoskeletal—aches in extremities, muscle aches Respiratory—dyspnea Dermatologic—rash, pruritus Urogenital—urinary frequency, disturbances of sexual function Other—gynecomastia, taste disorders

Drug Abuse and Dependence: No dependence or abuse has been reported

Overdosage: Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic Vital signs and fluid balance should be carefully monitored Adequate airway should be maintained and, if indicated, assisted respiration instituted No data are available on **Wytensin** dialyzability

Dosage and Administration: Individualize dosage A starting dose of 4 mg b i d is recommended, whether used alone or with a thiazide diuretic Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response Maximum dose studied has been 32 mg b i d , but doses this high are rarely needed

How Supplied: Wytensin Tablets, 4 mg and 8 mg, bottles of 100

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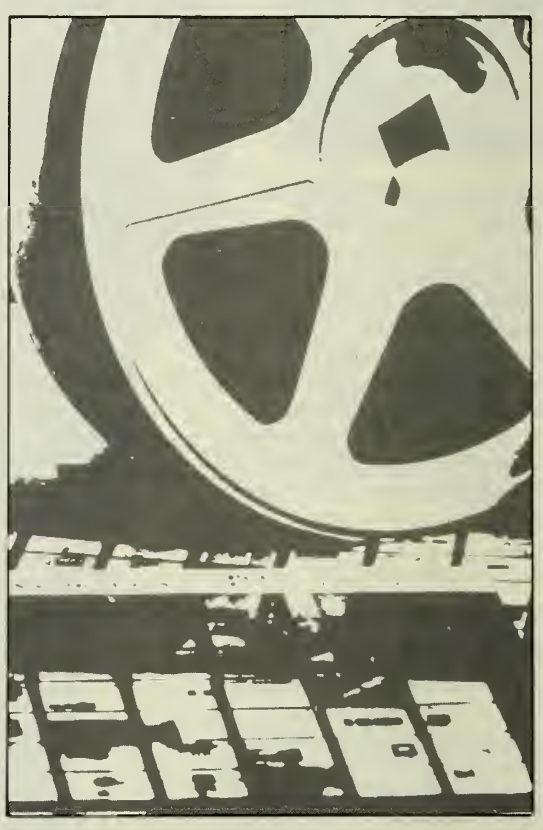

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ACUTE INFLAMMATION—Second Edition—J. V. Hurley, MD, PhD(Melb), FRCPath, Professor of Pathology, University of Melbourne. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 157 pages, $42.00.

CANCER OF THE CERVIX: DIAGNOSIS AND TREATMENT—Hugh M. Shingleton, MD, FACS, FACOG, Professor of Obstetrics and Gynecology; Associate Professor of Pathology, Division of Gynecologic Oncology, University of Alabama Medical Center; James W. Orr Jr., MD, Assistant Professor, Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Alabama Medical Center. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 233 pages, $19.75 (paperback).

CLINICAL BONE MARROW TRANSPLANTATION—Edited by Karl G. Blume, MD, Director, Department of Hematology and Bone Marrow Transplantation, and Lawrence D. Petz, MD, Chairman, Division of Medicine, City of Hope National Medical Center, Duarte, California. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 372 pages, $50.00.

CLINICAL DECISION LEVELS FOR LAB TESTS—Bernard E. Statland, MD, PhD, Director, Department of Laboratory Medicine, University Hospital, Boston, and Professor of Pathology and Medicine, Boston University Medical School. Medical Economics Books, Oradell, NJ 07649, 1983. 180 pages, $14.95, (paperback).

COMPUTERIZING YOUR MEDICAL OFFICE: A GUIDE FOR PHYSICIANS AND THEIR STAFFS—Dot Sellers, CMA-A. Medical Economics Books, Oradell, NJ 07649, 1983. 213 pages, $17.50, (paperback).

CONTROVERSIES IN NEURO-UROLOGY—David M. Barrett, MD, Associate Professor of Urology, Mayo Medical School, and Consultant in Urology, Mayo Clinic, Mayo Foundation, Rochester, Minnesota, and Alan J. Wein, MD, Professor and Chairman, Division of Urology, University of Pennsylvania School of Medicine, Philadelphia. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 537 pages, $75.00.

CURRENT EMERGENCY DIAGNOSIS & TREATMENT—Edited by John Mills, MD, Associate Professor of Medicine, Microbiology and Clinical Pharmacy, University of California, San Francisco, Chief of Infectious Disease Unit, San Francisco General Hospital; Mary T. Ho, MD, Assistant Professor of Medicine, University of Kentucky College of Medicine, Lexington; and Donald D. Trunkey, MD, Professor of Surgery, University of California, San Francisco, Chief of Surgery, San Francisco General Hospital; with associate authors. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 738 pages, $24.00.

ECHOCARDIOGRAPHIC DIAGNOSIS—DIFFERENTIAL DIAGNOSIS OF M-MODE AND TWO-DIMENSIONAL ECHOGRAPHIC APPEARANCES—Ivan A. D'Cruz, MD, FACC, FRCP(Edin), MRCP(Lond), Director, Echocardiography Section and Attending Physician, Michael Reese Hospital and Medical Center, Chicago, and Associate Professor of Medicine, University of Chicago, Pritzker School of Medicine. Macmillan Publishing Company, 866 Third Ave., New York, NY 10022, 1983. 434 pages. $49.95.

ECHOCARDIOGRAPHY—AN INTEGRATED APPROACH—Stephen Arvan, MD, Assistant Professor, Department of Medicine, University of Pittsburgh School of Medicine, and Head, Noninvasive Unit, Montefiore Hospital, Pittsburgh. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 503 pages, $60.00.

ENJOYING LIFE WITH EMPHYSEMA—Thomas L. Petty, MD, Professor of Medicine, Director, Webb-Waring Lung Institute, Co-Head, Division of Pulmonary Sciences, University of Colorado Health Sciences Center; Louise M. Nett, RN, RRT, Technical Director, Respiratory Care Unit, University of Colorado Health Sciences Center. Lea & Febiger, 600 South Washington Square, Philadelphia, PA 19106, 1983. 189 pages, $12.50, (paperback).

THE FOREMOST PHYSICIAN, THE FARSEEING PHYSICIAN—E. Ted Chandler, MD, Associate Professor, Department of Medicine, Bowman Gray School of Medicine, Wake Forest University; Robert L. Bloomfield, MD, Assistant Professor, Department of Medicine, Bowman Gray School of Medicine, Wake Forest University. Harbinger Medical Press, Box 17201, Winston-Salem, NC 27116, 1983. 87 pages, $8.95.

GENITOURINARY SURGERY—2 Volumes—Edited by David F. Paulson, MD, Professor of Urologic Surgery, Chief, Division of Urologic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 885 pages, $140.00.

HEPATOCELLULAR CARCINOMA—Edited by Kunio Okuda, MD, The First Department of Medicine, School of Medicine, Chiba University, Inohana, Japan; and Ian Mackay, MD, Head, Clinical Research Unit, Walter and Eliza Hall Institute, Royal Melbourne Hospital, Victoria, Australia. International Union Against Cancer, 3 rue du Conseil-Général, 1205 Geneva, Switzerland, 1982. 204 pages, $22.00, (paperback).

HYPOGLYCEMIA: FACT OR FAD?—WHAT YOU SHOULD KNOW ABOUT LOW BLOOD SUGAR—Lynn J. Bennion, MD, Member of the Clinical Faculty, Stanford University School of Medicine, Stanford, California. Crown Publishers, Inc., One Park Ave., New York, NY 10016, 1983. 176 pages, $12.95.

IMMUNOLOGICAL INVESTIGATION OF HUMAN VIRUS DISEASES—Volume 5 in Practical Methods in Clinical Immunology—Donald M. McLean, MD(Melbourne), FRCP(c), FRCPath, Professor, Division of Medical Microbiology, University of British Columbia, Vancouver. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 92 pages, $39.00.

IMMUNOLOGY—AN OUTLINE FOR STUDENTS OF MEDICINE AND BIOLOGY—Fifth Edition—D. M. Weir, MD, FRCPE, Reader in Immunology, Department of Bacteriology, University of Edinburgh Medical School. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 248 pages, $10,00 (softbound).

INFERTILITY IN THE MALE—Edited by Larry I. Lipshultz, MD, Professor of Urology, Baylor College of Medicine, Houston, and Stuart S. Howards, MD, Professor of Urology, University of Virginia School of Medicine, Charlottesville. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 391 pages, $52.00.

INFLAMMATORY BOWEL DISEASES—Edited by R. N. Allan, MD, PhD, FRCP, Consultant Physician, The General Hospital, Birmingham; M. R. B. Keighley, MS, FRCS, Consultant Surgeon, The General Hospital, Birmingham, and University of Birmingham; J. Alexander-Williams, MD, ChM, FRCS, FACS, Consultant Surgeon, The General Hospital, Birmingham, and Honorary Clinical Senior Lecturer, University of Birmingham, and Clifford Hawkins, MD, FRCP, Honorary Consultant Physician to the Queen Elizabeth Hospital, Birmingham, and Honorary Senior Clinical Lecturer in the University of Birmingham, England. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 575 pages, $85.00.

INTERNAL MEDICINE—Edited by Clarence A. Guenter, MD, Professor and Head, Department of Medicine, Faculty of Medicine, University of Calgary, and Director, Department of Medicine, Foothills Provincial General Hospital, Calgary, Alberta, Canada. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 863 pages, $25.00 (softbound).

KEY FACTS IN PULMONARY DISEASE—Edited by Om P. Sharma, MD, Professor of Medicine, and Oscar J. Balchum, MD, PhD, Hastings Professor of Medicine, University of Southern California School of Medicine, Los Angeles. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 572 pages, $37.50 (softbound).

MANAGING OB/GYN EMERGENCIES—Second Edition—Edited by John T. Queenan, MD, Professor and Chairman, Department of Obstetrics and Gynecology, Georgetown University School of Medicine, Washington, D.C., and Editor-in-Chief, Contemporary OB/GYN; and Coordinating Editor, Evelyn C. Gross, Editor, **Diagnosis** magazine. Medical Economics Books, 680 Kinderkamack Road, Oradell, NJ 07649, 1983. 290 pages, $29.50.

MANUAL OF CENTRAL VENOUS CATHETERIZATION AND PARENTERAL NUTRITION—Edited by J. L. Peters, FRCS, Resident Assistant Surgeon, University College Hospital, London. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 262 pages, $39.50.

MEDICAL ABBREVIATIONS HANDBOOK—2nd Edition—by the staff of Logical Communications. Medical Economics Books, Oradell, NJ 07649, 1983. 193 pages, $7.95 (softbound).

MEDICAL SPANISH: The Instant Survival Guide—Susan Lister and Cynthia W. Wilber. Addison-Wesley Publishing Company, Medical/Nursing Division, 2725 Sand Hill Rd., Menlo Park, CA 94025, 1983. 324 pages, $16.95 (softbound).

MEDICINE FOR THE PRACTICING PHYSICIAN—J. Willis Hurst, MD, Editor-in-Chief. Butterworth Publishers, 10 Tower Office Park, Woburn, MA 01801, 1983. 1,109 pages, $80.00.

METHODS IN HEMATOLOGY—Volume 6—The Thalassemias—Edited by D. J. Weatherall, MD, FRCP, FRCPath, FRS, Nuffield Professor of Clinical Medicine, University of Oxford; Honorary Director of the Medical Research Council Molecular Haematology Unit, John Radcliffe Hospital, Oxford, England. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 161 pages, $32.00.

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- ☐ No interaction with warfarin, theophylline or diazepam.
- ☐ Headache has been reported in about 3% of patients.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers. Despite some similarities in pharmacokinetics, after 10-12 hours Zantac 150 mg still provides a 40% reduction in acid output compared to 1% for cimetidine 300 mg, thus providing a rationale for b.i.d. dosing.

** 37% of patients can be expected to show complete healing at the end of two weeks; if healing is confirmed, treatment can be discontinued.

Glaxo ROCHE

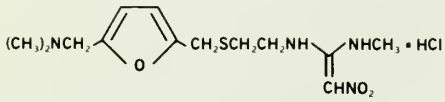
Please see complete prescribing information on the following page.

The first advance in H_2-antagonist therapy

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTION: The active ingredient in ZANTAC® Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure:



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLOGY: ZANTAC® (ranitidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. **Effects on acid secretion:**
ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC® on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. **Effects on other gastrointestinal secretions:**
Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.
Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. **Other pharmacological actions:**
a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. **Pharmacokinetics:**
ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:
Duodenal Ulcer
In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC®-treated patients as shown below.

	ZANTAC® +		Placebo +	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid	
	Ulcer Healed	Ulcer Not Healed
ZANTAC®	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIONS AND USAGE:
ZANTAC® (ranitidine hydrochloride) is indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC® (ranitidine hydrochloride).

PRECAUTIONS:
General
1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests
False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction
Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility
There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. Coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy
Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC® (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in children have not been established.

Use in Elderly Patients
Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS
Headache has been found to be more frequent in ZANTAC®-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC® in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:
Duodenal Ulcer
The current recommended adult oral dosage of ZANTAC® for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED
ZANTAC® Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

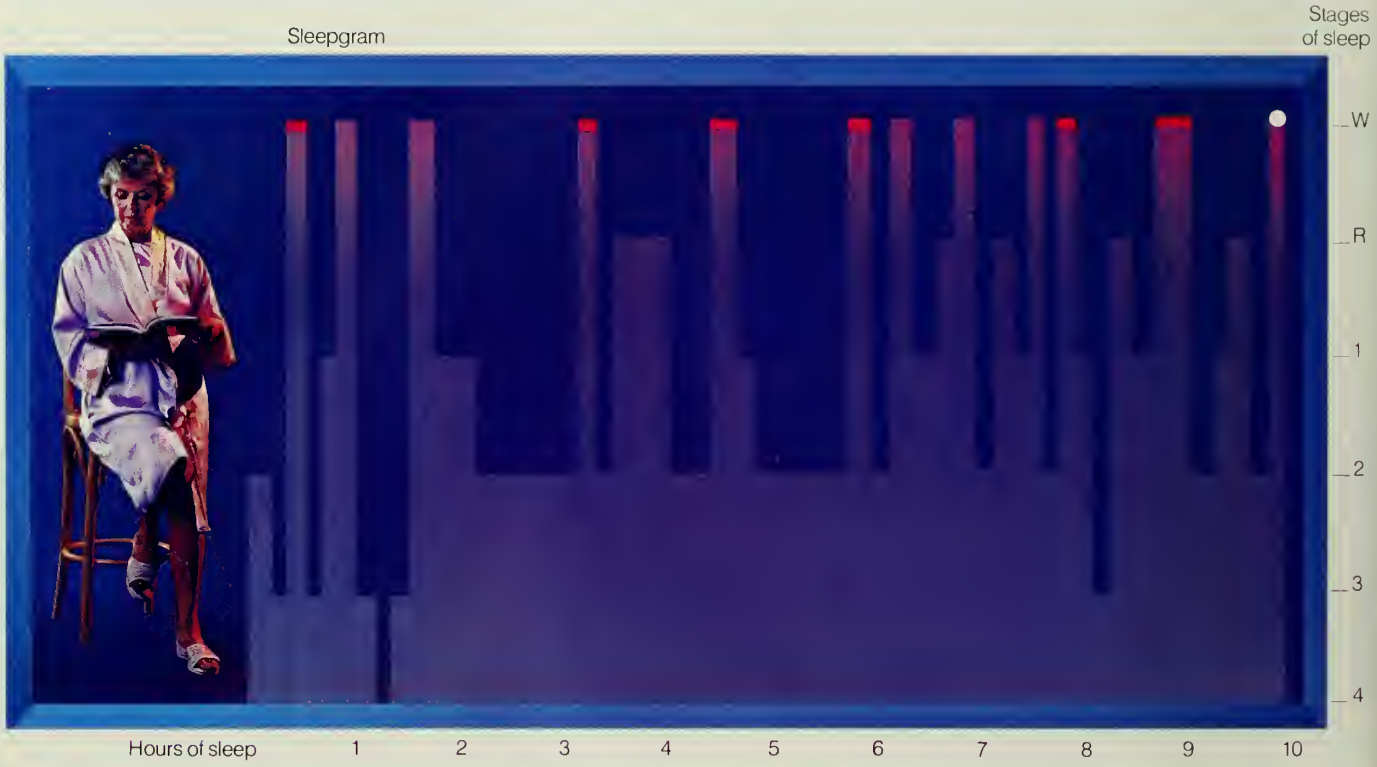
Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

DISRUPTIVE
DISTRESSING
DISABLING

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

■ = objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

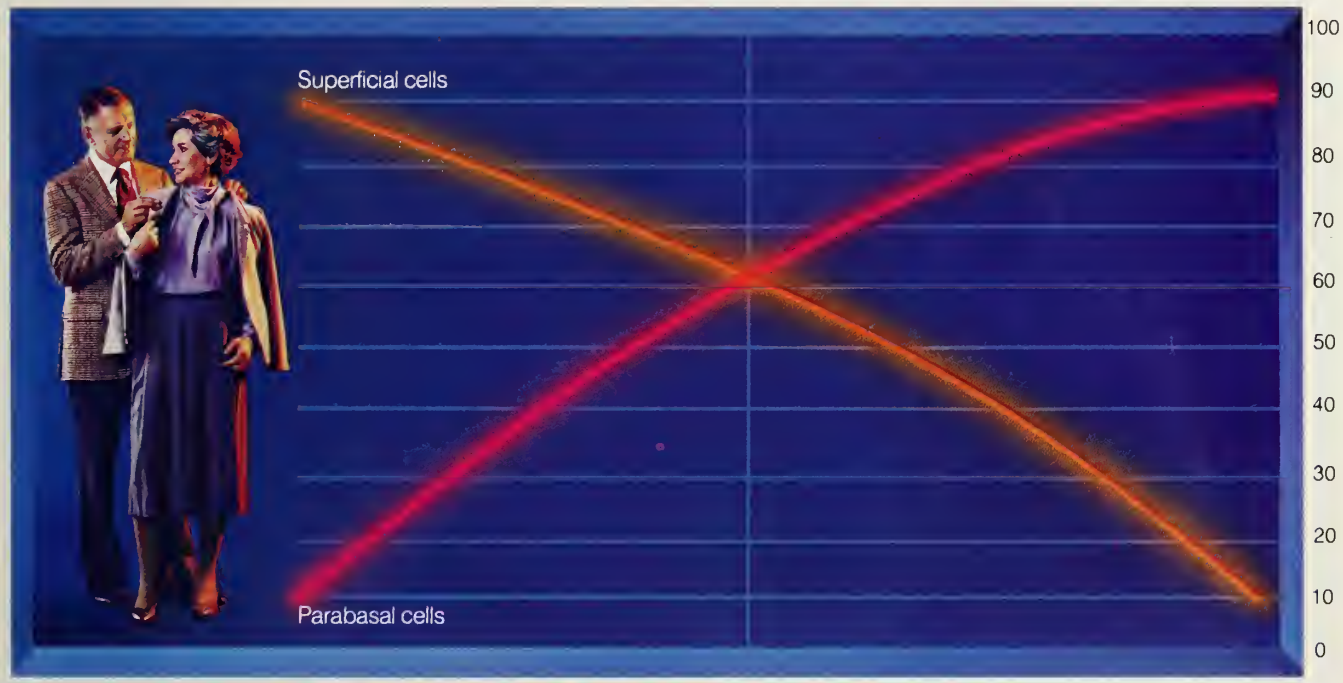
FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories

THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

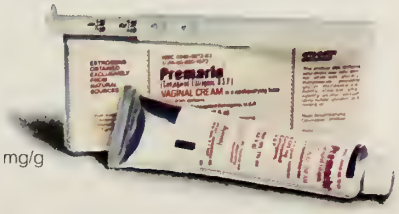
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

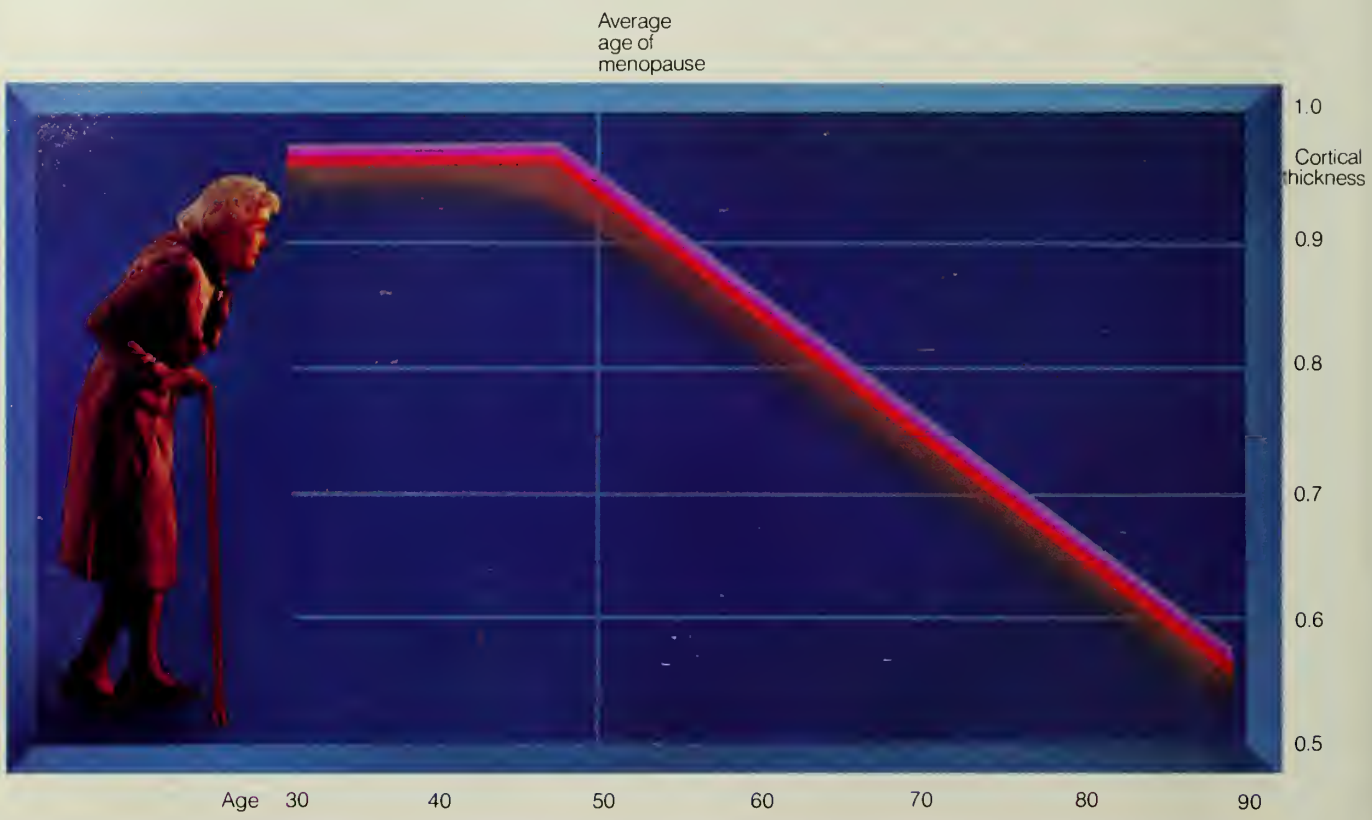
FOR ATROPHIC VAGINITIS

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/g

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

Please see last page for brief summary of prescribing information.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance; aggravation of porphyria, edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube.

REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al: Estrogen replacement therapy: Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull*, June 1983, pp 1-5. 4. Ayers LJ: The maturation index: A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G: Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ: Age, estrogen, and bone density. *Clin Obstet Gynecol* 19B1;24:203-21B. 7. Gordan GS, Picchi J, Roof BS, et al: Postmenopausal osteoporosis. *Am Fam Physician* 1973;B:74-B3. B. US Bureau of the Census, *Statistical Abstract of the United States* 19B2-B3, ed 103. Washington, DC, US Dept of Commerce, 1982, p 25. 9. Mallette LE: Osteoporosis: Approaching treatment with optimism. *Postgrad Med* 1982;72:271-27B

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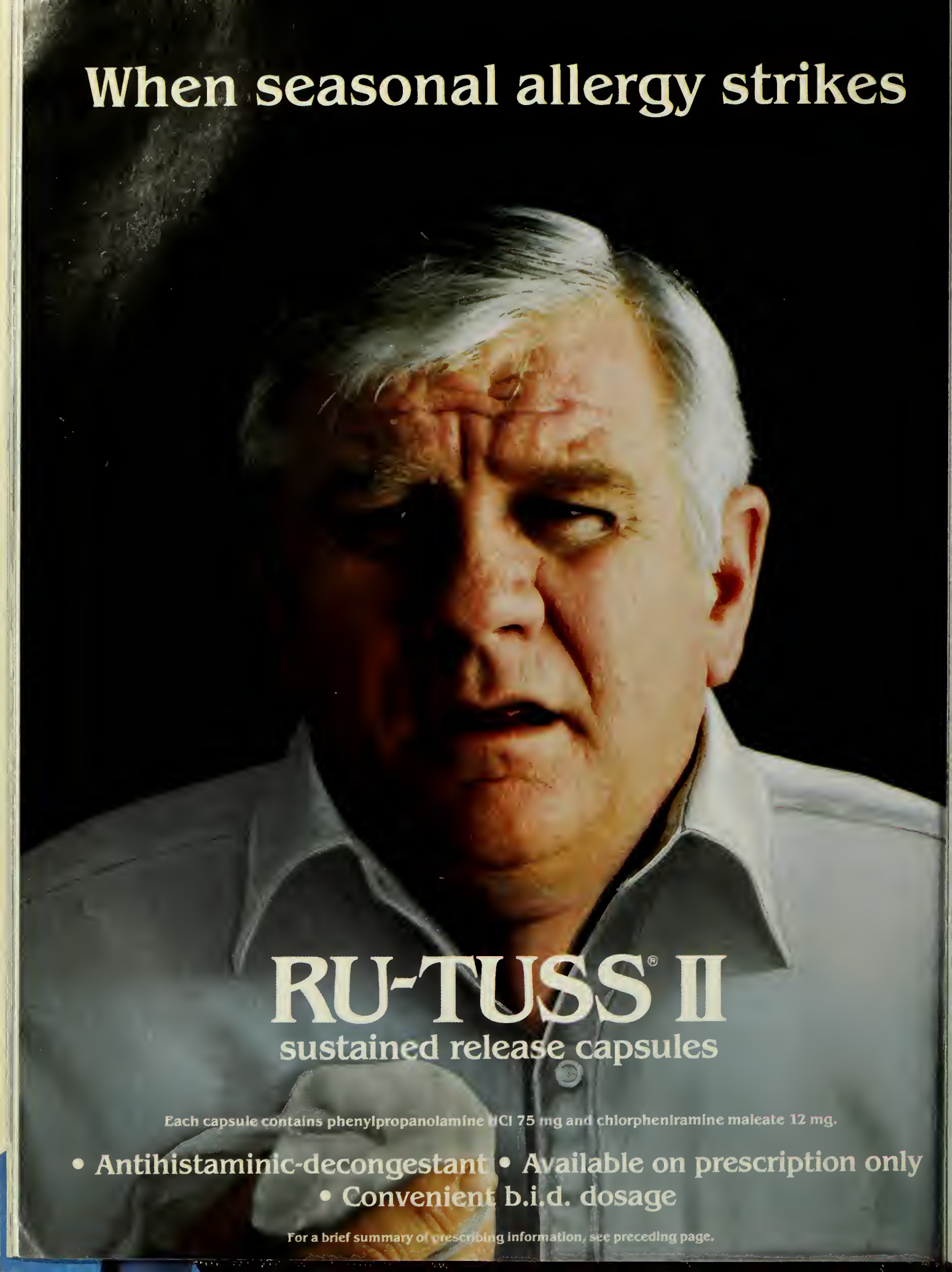
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For a brief summary of prescribing information, see preceding page.

RU-TUSS® II

sustained release capsules

Before prescribing, see complete prescribing information. The following is a brief summary.
DESCRIPTION: Each sustained release capsule contains 12 mg of chlorpheniramine maleate, USP and 75 mg of phenylpropanolamine hydrochloride, USP in a base to provide prolonged activity.
INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).
CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.
WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.
Usage in pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.
PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.
ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with chlorpheniramine maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, hypertension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis, leukopenia.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis hysteria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.
DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.
OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.
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ALLERGY AND IMMUNOLOGY

June 13-15—**Contemporary Aspects of Clinical Immunology.** American Society of Clinical Pathologists at San Diego. Wednesday-Friday. 18.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

ANESTHESIOLOGY

June 14-17—**Annual Scientific Meeting of the California Society of Anesthesiologists** at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

September 28-30—**Anesthesia Practice 1984.** Anesthesiology Education Foundation at Monterey. Friday-Sunday. 10½ hrs. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

CANCER

May 18-20—**The Primary Care Physician and Cancer.** UCSD at Vacation Village, San Diego. Friday-Sunday.

June 22—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. $135. Contact: J. Shiller, CMEA, P.O. Box 94296, San Diego 92138. (619) 223-2997.

June 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. $135. Contact: J. Shiller, CMEA, P.O. Box 84296, San Diego 92138. (619) 223-2997.

CARDIOLOGY

April 18-20—**Moguls of Cardiology.** American Heart Association, Golden Empire Chapter at Caesars Tahoe, Lake Tahoe. Wednesday-Friday. Contact: AHA, Golden Empire Chapt., P.O. Box 160126, 1727 30th St., Sacramento 95816. (916) 454-0701.

April 28—**50,000 Open-Heart Operations.** See Surgery, April 28.

May 4-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Sheraton Palace, San Francisco. Friday-Sunday. Contact: IMEC, Div. of Postgraduate and CME, 64 Inverness Dr. E., Englewood, CO 80112.

May 5-6—**Advanced Industrial Pulmonary Function Testing.** UCLA. Saturday-Sunday. 12 hrs. $190.

May 12—**Cardiac Surgery Research.** See Surgery, May 12.

May 12—**Cardiovascular Symposium.** Marian Medical Center at Holiday Inn, Santa Maria. Saturday. 6 hrs. Contact: Alfred Sanfilippo, MD, Dir. CME, Marian Med. Ctr., 1400 E. Church, Santa Maria 93454. (805) 922-5811, ext. 115.

(Continued on Page 547)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, Center for Health Education, 2801 Atlantic Ave., (P.O. Box 1428), Long Beach 90801. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
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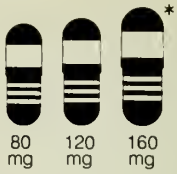

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length and diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the arteries of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily in angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

Just once each day for initial therapy in

(Continued from Page 543)

May 18-20—**Decision Making in Congenital Heart Disease.** Children's Hospital and Health Center and Donald N. Sharp Memorial Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Sunday. 18 hrs. $350. Contact: Congenital Heart Disease, P.O. Box 9494, San Diego 92109. (619) 272-3126.

May 21-22—**Advanced Cardiac Life Support.** See Emergency Medicine, May 21-22.

June 10-13—**Advanced Echocardiography—1984: Interactions with NMR, Digital Angiography and CT Scanning.** American College of Cardiology at San Diego. Sunday-Wednesday. Contact: Reg. Sec., Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 22-24—**ECG Interpretation, Arrhythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at Lake Tahoe. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 22-24—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Scott and Klamath Rivers. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., P.O. Box 6009, Redding 96099-6009. (916) 243-2121.

June 25-27—**Cardiac Morphology: Echocardiographic, Nuclear Imaging, Necropsy Correlations.** American College of Cardiology and Indiana University School of Medicine at Hyatt Lake Tahoe, Incline Village. Monday-Wednesday. Contact: Reg. Sec., Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 25-29—**National Board Review Course in Pulmonary Medicine.** American College of Chest Physicians at Sheraton Palace Hotel, San Francisco. Monday-Friday. 28 hrs. Contact: Dept. of Ed., ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (312) 698-2200.

August 12-17—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

August 17-19—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., P.O. Box 6009, Redding 96099-6009. (916) 243-2121.

August 24-26—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress and Holter) and Cardiac Resuscitation.** International Medical Education Corporation at Monterey. Friday-Sunday. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 14-16—**ECG Interpretation, Arrhythmia, and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 15-22—**Hawaiian Echocardiography Course.** Institute for Medical Studies at Hawaiian Islands. One week. 20 hrs. $295. Contact: IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

September 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Meridien Hotel, San Francisco. Thursday-Saturday.

EMERGENCY MEDICINE

April 30-May 4—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday.

May 4-5—**1st Annual Emergency Symposium.** Southern California Kaiser-Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. 11 hrs. $150. Contact: Dept. of Clinical Services, SCKPM Care Program, 4747 Sunset Blvd., Los Angeles 90027.

May 21-22—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

May 29-June 2—**Gateway to Knowledge.** Society of Critical Care Medicine at San Francisco. Tuesday-Saturday. Contact: SCCM, 223 E. Imperial Hwy, Ste. 110, Fullerton 92635. (714) 870-5243.

June 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 33 hrs.

June 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton Wharf, San Francisco. Monday-Friday. $425.

July 4-5—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Salmon River. Wednesday-Thursday. 10 hrs. $245. Contact: Mercy Medical Center, Dept. of Cont. Ed., P.O. Box 6009, Redding 96099-6009. (916) 243-2121.

July 6-8—**Trauma and CPR Update—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 10-13—**Emergency Medicine: A Critical Appraisal.** California Chapter American College Emergency Physicians and Emergency Medical Associates at Ramada Inn at Fisherman's Wharf, San Francisco. Tuesday-Friday. 20 hrs. $360. Contact: Seminars International, Dept. A, 15910 Ventura Blvd., Ste. 731, Encino 91436.

July 16-20—**Postgraduate Institute for Emergency Physicians.** UCSD. Monday-Friday. 33 hrs.

July 30-31—**Advanced Cardiac Life Support.** Emergency Care Education Center, Emergency Department Physicians, and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina Del Rey 90291. (213) 822-1312.

August 3-5—**Whitewater Raft Conference: Trauma Evaluation and Treatment.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., P.O. Box 6009, Redding 96099-6009. (916) 243-2121.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** American College of Obstetrics and Gynecology at Hotel del Coronado, Coronado. Wednesday-Friday. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington DC 20024.

August 24-26—**Wilderness Emergency Care—Mt. Shasta Summit Expedition.** Mercy Medical Center, Redding at Mt.

(Continued on Page 549)

"WHAT A LOUSY TIME TO COUGH."

Your patient deserves a totally effective cough and cold remedy that only you can prescribe.

Cough or cold, there's a form of Citra Forte to help your patients *feel* better, as well as *get* better. And since Citra Forte Syrup and Capsules are both "prescription-only" your patients get the added assurance that comes with "doctor-only" medication.

Citra Forte is the "total" cough and cold remedy. The pleasant tasting syrup provides antitussive and antihistaminic action; while the convenient capsules are also antitussive and antihistaminic, with decongestant and analgesic activity to relieve cold symptoms.

There may be no "good" time for a cough or cold, but anytime a patient has either one is a good time for Citra Forte...syrup or capsules

CITRA® FORTE SYRUP (C III)

Each 5cc contains:

Hydrocodone Bitartrate (WARNING: May be habit forming)	5 mg.
Ascorbic Acid	30 mg.
Pheniramine Maleate	2.5 mg.
Pyrilamine Maleate	3.33 mg.
Potassium Citrate	150 mg.

CITRA® FORTE CAPSULES (C III)

Hydrocodone Bitartrate (WARNING: May be habit forming)	5 mg.
Ascorbic Acid	50 mg.
Pheniramine Maleate	6.25 mg.
Pyrilamine Maleate	8.33 mg.
Chlorpheniramine Maleate	1 mg.
Phenylephrine HCl	10 mg.
Salicylamide	227 mg.
Caffeine Alkaloid	30 mg.
Acetophenetidin	120 mg.

PRECAUTIONS: Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.

CITRA FORTE CAPSULES should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism. WARNING: This preparation may damage the kidneys when used in large amounts or for a long period of time. Use with caution in greater than recommended dose or regularly for longer than 10 days (Acetophenetidin).

BOYLE

Boyle & Company/
Pharmaceuticals
13260 Moore Street,
Cerritos, CA 90701

83-28-0940

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Shasta. Friday-Sunday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

August 27-31—**Topics in Emergency Medicine.** UCSF at San Francisco. Monday-Friday. $425.

September 1-3—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Klamath River. Saturday-Monday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., P.O. Box 6009, Redding 96099-6009. (916) 243-2121.

September 28-29—**Advanced Trauma Life Support Provider Course.** Emergency Shock Trauma Institute, Mercy Hospital at San Diego. Friday-Saturday. 16 hrs. $475. Contact: Emergency Shock Trauma Institute, Mercy Hospital, 4077 5th Ave., San Diego 92103. (619) 294-8111.

INTERNAL MEDICINE

April 26-27—**3rd Annual Bright Horizons in Respiratory Care.** Annenberg Center for Health Sciences, Rancho Mirage. Thursday-Friday. 9 hrs. Contact: Annenberg Center for Health Sciences-A, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

April 28-May 5—**New Concepts in Gastroenterology: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Poplin Creek Estate, Ojai. One week. 24 hrs. Contact: Richard F. Paris, MD. (208) 788-4995.

May 4-6—**Annual Meeting of the California Society of Internal Medicine** at Doubletree Inn, Monterey. Friday-Sunday. Contact: CSIM, 703 Market St., Ste. 1412, San Francisco 94103.

May 5-13—**Endocrinology in Clinical Practice.** UCSF. One week.

May 7-11—**Advances in Internal Medicine.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

May 7-11—**Clinical Microbiology Update.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 29.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-1336, ext. 129.

May 20-26—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** American Institute of Primary Care Medicine, University of Arizona College of Medicine at Napa Valley. One week. 24 hrs. Contact: Richard F. Paris, MD, P.O. Box 209, Sun Valley, ID 83353. (208) 788-4995.

June 13-15—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Stanford Court Hotel, San Francisco. Wednesday-Friday. $375.

June 18-22—**Advances in Internal Medicine.** UCSF at Hyatt Regency, San Francisco. Monday-Friday. $465.

June 22-24—**Update on Cardiovascular Drugs—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 7-14—**32nd Annual Intensive Review of Internal Medicine.** USC. One week. $475.

July 20-22—**Infectious Disease.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 29-August 1—**Biomedical Ethics—Wilderness Horseback Conference.** Mercy Medical Center, Redding at Trinity Alps Wilderness. Sunday-Wednesday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

August 17-19—**2nd Annual La Jolla Summer Conference on Dermatology, Immunology and Rheumatology.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. Contact: Dianne Tisue, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

September 10-15—**6th Comprehensive Nephrology Review Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Saturday. 38.5 hrs. $695.

September 15—**Neurology.** UCSF at Fresno. Saturday.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 19—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. Contact: Charles R. Beeson, MD, Assoc. Chief of Staff for Ed., VA Medical Center, 16111 Plummer St., Sepulveda 91343. (818) 891-2374.

OBSTETRICS AND GYNECOLOGY

April 16-19—**Diagnostic Cytology of the Female Genital Tract.** American Society of Clinical Pathologists at San Francisco. Monday-Thursday. 22.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

April 27-28—**29th Annual T. Hart Baker MD Obstetrics and Gynecology Symposium.** Southern California Kaiser-Permanente Medical Care Program at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

May 5-10—**32nd Annual Clinical Meeting of American College of Obstetrics and Gynecology** at San Francisco. Saturday-Thursday. 17 hrs. Contact: ACOG, Registrar, Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

May 13-16—**Recent Advances in Obstretrics and Gynecology.** UCSD. Sunday-Wednesday.

May 30-June 2—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center and UCI at Silverado Country Club and Resort, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

August 9-11—**Basic and Advanced Colposcopy.** American College of Obstetrics and Gynecology at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E., 600 Maryand Ave., SW, Washington, DC 20024.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

OPHTHALMOLOGY

May 12—**Contact Lens Practice in the Mid-80's.** Jules Stein Eye Institute, Los Angeles. Saturday. $100. Contact: Lu Hendricks, Academic Program Admin., JSEI, UCLA School of Medicine, Center for the Health Sciences, Los Angeles 90024.

June 7-8—**Practical Office Management of Corneal, External Diseases and Uveitis.** UCSF at Hyatt Regency, San Francisco. Thursday-Friday.

June 8-9—**Microsurgery and Laser Techniques for Glaucoma.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 14 hrs. $500. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024.

June 14-16—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. 18 hrs. $750. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024.

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** See Pediatrics, June 29-30.

PEDIATRICS

April 25-27—**9th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center and UCI at Hyatt Regency, Long Beach. Wednesday-Sunday. 17 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

April 26-28—**Advances in Pediatrics.** UCSF at Mark Hopkins, San Francisco. Thursday-Saturday.

April 27-29—**Pediatric Infectious Disease.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Friday-Sunday. Contact: AAP, Div. of Cont. Ed., P.O. Box 1034, Evanston, IL 60204.

May 7-11—**The 1984 14th Annual Review of Pediatrics.** USC and Children's Hospital of Los Angeles at Los Angeles. Monday-Friday. 26 hrs. $350. Contact: USC.

May 16—**Los Angeles Pediatric Society Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** See Psychiatry, May 17-18.

May 26-28—**1984 Annual Spring Meeting Northern California Chapter American Academy of Pediatrics** at Hyatt Del Monte, Monterey. Saturday-Monday. 11 hrs. Contact: AAP, 1125 A St., Ste. 210, San Rafael 94901. (415) 459-4775.

June 13—**Seizure Disorders in Infancy and Childhood.** LLU. Wednesday. 4 hrs. $50.

June 28-30—**9th Annual Meeting of the Society for Pediatric Dermatology.** STAN at Caesar's Tahoe, Lake Tahoe. Thursday-Saturday.

(Continued on Page 556)

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104 672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PRDCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e g , where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCAROIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCAROIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PRDCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PRDCARDIA and a beta blocker, but the possibility that it may occur with PROCAROIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PRDCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PRDCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA

Congestive Heart Faifure: Rarely, patients, usually receiving a beta blocker, have developed heart failure affer beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PRDCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PRDCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due fo associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGDT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease affer about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature

HDW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PRDCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. © 1982, Pfizer Inc.

Pfizer LABORATORIES DIVISION
PFIZER INC

"I can do things that I couldn't do for 3 yrs. including joining the human race again."

Quotes from an unsolicited letter received by Pfizer from an angina patient
While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree

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"My daily routine consisted of sitting in my chair trying to stay alive."

"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

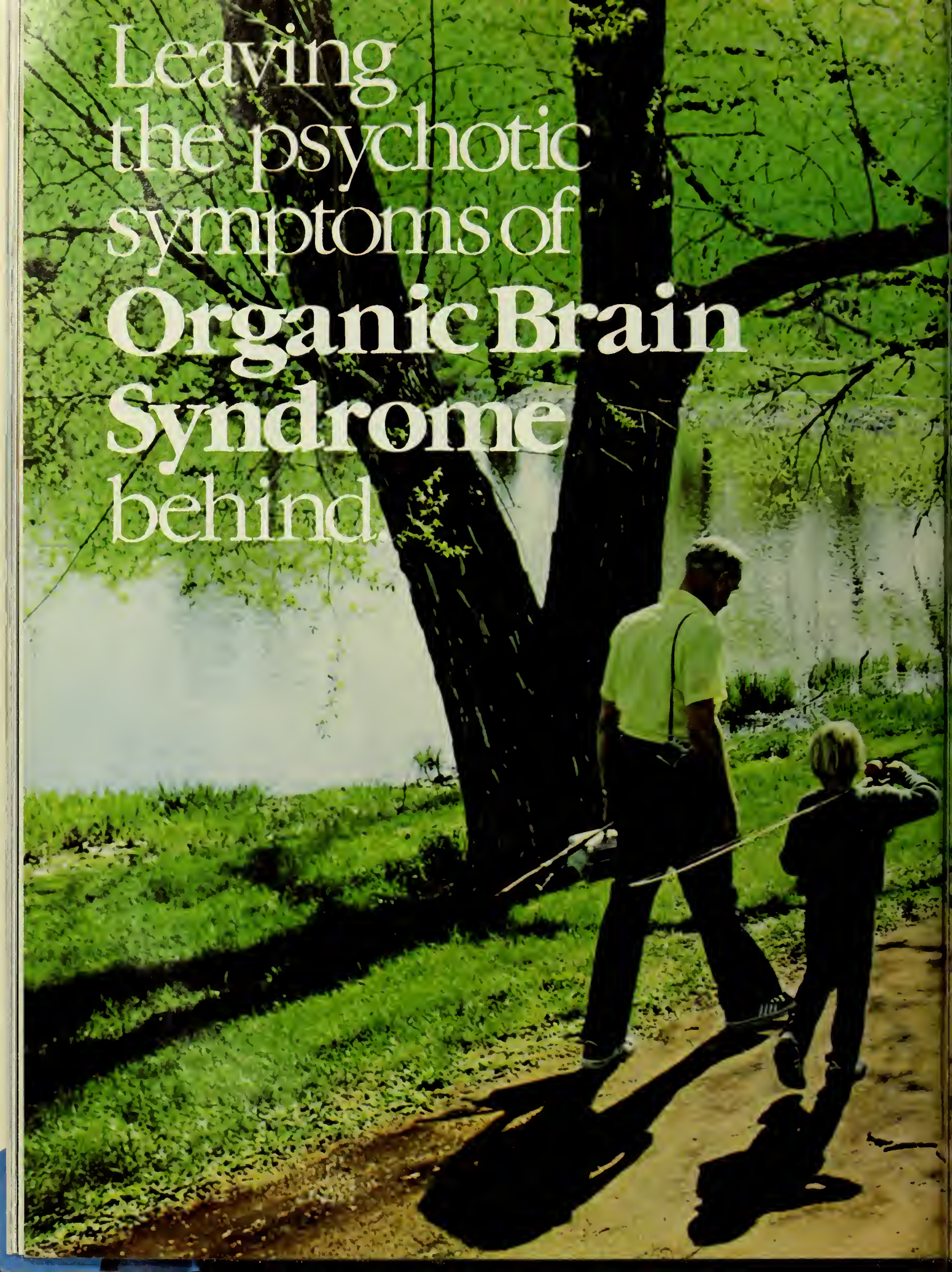
Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

for the varied faces of angina

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*


Leaving
the psychotic
symptoms of
Organic Brain
Syndrome
behind.

Effective

Treatment with Navane can produce improvement in psychotic symptoms such as hallucinatory behavior and unusual thought content as well as hostility, disorientation and depressive mood,[1,2] leaving the elderly patient more alert[2] and better able to participate in the activities of family life.

Well tolerated

Navane is generally well tolerated by elderly patients. Excessive sedation or drowsiness has been reported, but is uncommon.[1] Anticholinergic effects[3] and hypotension[4,5] are reported, but rarely. Should they occur, extrapyramidal symptoms can usually be readily controlled.

Navane®

(thiothixene) (thiothixene HCl)

Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
Concentrate 5 mg/ml Intramuscular 2 mg/ml, 5 mg/ml

See following page for a brief summary of prescribing information.

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at the forefront of psychopharmacology

Navane®

(thiothixene) (thiothixene HCl)

References 1. Util TM, Unverdi C, Wohlrade J, et al: Drug therapy of psychosis associated with organic brain syndrome. Presented as a Scientific Exhibit at the American Public Health Association Centennial, Atlantic City, New Jersey, November 12-16, 1972. 2. Katz MM, Util TM. Video methodology for research in psychopathology and psychopharmacology. *Arch Gen Psychiatry* 31:204-210, 1974. 3. Ketai R: Psychotropic drugs in the management of psychiatric emergencies. *Postgraduate Medicine* 58:87-93, 1975. 4. Birkett DP, Hirschfield W, Simpson GM. Thiothixene in the treatment of diseases of the senium. *Curr Ther Res* 14:775-779, 1972. 5. Data on file at Roerig

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Usage in Pregnancy*—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels, the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane. These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane (thiothixene). Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

There is no known effective treatment for tardive dyskinesia, antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear.

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Hepatic effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene) have been reported.

Hematologic effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other adverse reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea; increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

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(Continued from Page 550)

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Saturday. 8 hrs. $100.

PSYCHIATRY

April 27-28—**Family Violence and Violent Interactions.** Mental Research Institute, Palo Alto. Friday-Saturday. 6 hrs. $85. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

April 28-29—**The Cutting Edge—1984: The Psychotherapy of Borderline and Narcissistic Disorders.** UCSD at Hotel del Coronado, San Diego. Saturday-Sunday. 13 hrs. $250.

May 3-6—**28th Annual Meeting of the American Academy of Psychoanalysis** at Hyatt Regency Hotel, Los Angeles. Thursday-Sunday. Contact: AAP, 30 E. 40th St., Ste. 608, New York, NY 10016. (212) 697-4105.

May 5—**The Skills of Family Therapy Supervision.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 9-11—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 12—**Treating Depression in a Marital Context.** Mental Research Institute, Palo Alto. Saturday. 5 hrs. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 14-17—**Family Crisis: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** UCD at Holiday Inn Holidome, Sacramento. Thursday-Friday.

May 19—**Conception and Misconceptions of Structural Family Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 19-20—**Freud-Jung Symposium: Clinical Issues.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday.

June 8—**8th Annual Psychiatry Symposium.** Southern California Kaiser-Permanente Medical Group at Newport Beach Marriott Hotel. Friday. 6 hrs. $100. Contact: Dept. of Clinical Services, SCKPMG, 4747 Sunset Blvd., Los Angeles 90027.

June 9—**Brief Therapy with Child and Adolescent Problems.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

June 16—**Clinical Decision-Making with Couples and Families.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

June 18-22—**Divorce Mediation.** Mental Research Institute, Palo Alto. Monday-Friday. 20 hrs. $195. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 14—**The Interactional Treatment of Eating Disorders.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $95. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 20-21—**Human Sexuality for the Health Professional.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 23-27—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 28—**Treating Depression in a Marital Context.** Mental Research Institute, Palo Alto. Saturday. 5 hrs. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 29-August 2—**Mental Research Institute Summer Seminar** at Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-8—**Basic Hypnotherapy: Principles and Applications.** Mental Research Institute, Palo Alto. Monday-Wednesday. 6 hrs. $65. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-10—**Brief Therapy.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $175. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 13-16—**Family Crisis: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 18-23—**Responsibility Issues in Mental Health.** Southern California Psychiatric Institute at Mauna Kea Beach Hotel, Kauela, HI. Saturday-Thursday. 15 hrs. Contact: Gail Waldron, MD, Program Dir., SCPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

August 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 25—**Case Studies in Brief Interactional Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

RADIOLOGY AND PATHOLOGY

April 16-19—**Diagnostic Cytology of the Female Genital Tract.** See Obstetrics and Gynecology, April 16-19.

April 23-27—**Review in Immunohematology and Blood Banking.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 31.5 hrs. Contact: Regional Educational Activities, 2100 W. Harrison St., Chicago, IL 60612. (312) 738-1336, ext. 129.

April 29-May 4—**4th Annual Residents' Radiology Review Course.** UCSD. Sunday-Friday. 37 hrs. $360.

May 4-6—**California Radiological Society 1984 Annual Meeting** at Del Monte Hyatt House, Monterey. Friday-Sunday. 11.5 hrs. Contact: CRS, 1225 8th St., Ste. 590, Sacramento 95814. (916) 446-2028.

May 7-11—**Clinical Microbiology Update.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 29.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

(Continued on Page 558)

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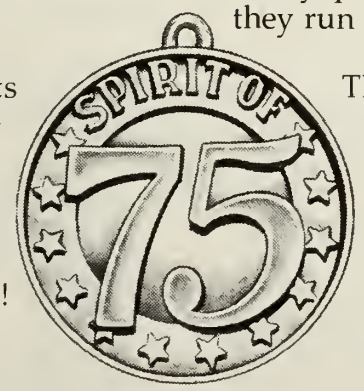

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(Continued from Page 556)

May 7-11—**San Diego Imaging Symposium.** UCSD. Monday-Friday. 27 hrs. $400.

May 22-25—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Tuesday-Friday. 26 hrs. Contact: R. S. Pakusch, MD, Program Chairman. (415) 561-3764.

June 8-10—**9th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $290. Contact: Richard A. Oas, MD, SDUC, % LARS, 5200 Century Blvd., Ste. 920, Los Angeles 90045. (213) 484-5120.

June 10-16—**4th Annual Post Conference Seminar.** American College of Radiology at Silverado Country Club, Napa Valley. One week. 20 hrs. $350. Contact: Richard A. Oas, MD, SDUC, % LARS, 5200 Century Blvd., Ste. 920, Los Angeles 90045. (213) 484-5120.

June 13-15—**Contemporary Aspects of Clinical Immunology.** American Society of Clinical Pathologists at San Diego. Wednesday-Friday. 18.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

June 17-22—**Pathology of the Lung.** UCSD. Sunday-Friday. 50 hrs.

August 14-18—**Radiology Physics Review Course.** UCD at Sacramento. Tuesday-Saturday.

August 20-24—**Radiology of the Abdomen.** UCSD at San Diego and Anaheim. Monday-Friday. 27 hrs. $395.

September 17-20—**American College of Radiology Meeting** at Century Plaza Hotel, Los Angeles. Monday-Thursday. Contact: ACR, 20 N. Wacker Dr., Chicago 60606. (312) 236-4963.

SPORTS MEDICINE

May 2-6—**Mountain Medicine: 1984.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Friday-Tuesday.

May 23-26—**American College of Sports Medicine Meeting** at Town and Country Hotel, San Diego. Monday-Thursday. Contact: T. Miller, Exec. Dir., ACSM, 1440 Monroe St., Madison, WI 53706.

June 14-16—**Knee Problems in Athletes.** American Academy of Orthopaedic Surgeons at Monterey. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

June 24-27—**Marine Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Wednesday.

July 20-22—**Sports Medicine and Cardiovascular Fitness—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

July 23-26—**10th Annual Meeting of American Orthopaedic Society for Sports Medicine** at Marriott Hotel, Anaheim. Monday-Thursday. Contact: AOSSM, P.O. Box 94274, Chicago 60690.

SURGERY

April 19-21—**Nasal Plastic and Reconstructive Surgery.** Pacific Medical Center, San Francisco. Thursday-Saturday. 15 hrs. $350. Contact: Div. of Ed., Presbyterian Hospital of Pacific Medical Center, P.O. Box 7999, San Francisco 94120.

April 28—**50,000 Open-Heart Operations.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Saturday. 2 hrs. Contact: Heart Institute of the Desert, Wright Bldg., Ste. 406, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

May 3-5—**The Wrist.** American Academy of Orthopaedic Surgeons at Newport Beach. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

May 6-9—**American Association of Plastic Surgeons Meeting** at Hotel del Coronado, Coronado. Sunday-Wednesday. Contact: AAPS, Div. of Plastic Surgery, School of Medicine, Univ. of No. Carolina, Chapel Hill, NC 27514. (919) 966-3080.

May 9—**Surgery.** LLU. Wednesday. 4 hrs $50.

May 12—**Cardiac Surgery Research.** Eisenhower Medical Center at Annenberg Center for Health Sciences, Rancho Mirage. Saturday. 2 hrs. Contact: Heart Institute of the Desert, Wright Bldg., Ste. 406, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

May 13-25—**Temporal Bone Surgical Dissection 1984.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

May 14-18—**Microsurgery Training Workshop.** Microsurgery Education and Research Foundation at La Jolla Village Inn, La Jolla. Monday-Friday. 35 hrs. $1,300. Contact: Hazel Sayers, Workshop Coord., P.O. Box 22514, San Diego 92122.

May 21-25—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 1-3—**Failed Arthroplasty Revision and Salvage.** American Academy of Orthopaedic Surgeons at San Francisco. Friday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

June 4-8—**Microsurgery Training Workshop.** Microsurgery Education and Research Foundation at La Jolla Village Inn, La Jolla. Monday-Friday. 35 hrs. $1,300. Contact: Hazel Sayers, Workshop Coord., P.O. Box 22514, San Diego 92122.

June 9-14—**Fingers to the Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Saturday-Thursday.

June 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 20-24—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Regency, Maui. Wednesday-Sunday. Contact: WTSA, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

June 21-23—**Gynecologic Surgery: Principles and Techniques.** American College of Obstetrics and Gynecology at Silverado, Napa. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

June 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

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August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 20-22—**Microsurgery: An Introduction to Microtechnique for Small Artery and Nerve Repair.** American Academy of Orthopaedic Surgeons at San Diego. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

OF INTEREST TO ALL PHYSICIANS

April 23-26—**Alcoholism and Drug Addiction Intervention Workshop.** Scripps Memorial Hospital, La Jolla. Monday-Thursday. $165. Contact: Meeting Management, 3770 Tansy, San Diego 92121. (619) 453-6222.

April 25-26—**Research in Continuing Medical Education.** UCSF. Wednesday-Thursday.

April 28—**Eating Disorders in the Young Adult: Obesity and Anorexia.** Children's Hospital Medical Center, Oakland. Saturday. 5 hrs. $25. Contact: Mr. Eddie Burden, Teen Clinic—Bldg. J, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3387.

April 28-29—**Basic Curriculum.** American Occupational Medicine Association at Los Angeles. Saturday-Sunday. 15 hrs. Contact: AOMA, 2340 S. Arlington Heights Rd., Arlington Heights, IL 60005.

April 29-May 5—**American Occupational Health Conference** at Los Angeles. One week. Contact: AOMA, 2340 S. Arlington Heights Rd., Arlington Heights, IL 60005.

May 5-12—**Challenges in Acute Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Poplin Creek Estate, Ojai. One week. Contact: Richard F. Paris, MD. (208) 788-4995.

May 6-10—**55th Annual Scientific Meeting of the Aerospace Medical Association** at San Diego. Sunday-Thursday. 24 hrs. Contact: ASMA, Washington National Airport, Washington, DC 20001.

May 14-18—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

May 18-20—**The Primary Care Physician and Cancer.** See Cancer, May 18-20.

May 19-20—**12th Annual Family Practice Symposium.** Southern California Permanente Medical Group at Sheraton Universal Hotel, North Hollywood. Saturday-Sunday. 11 hrs. Contact: SCPMG, Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

May 20-25—**Family Practice Refresher Course.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Friday.

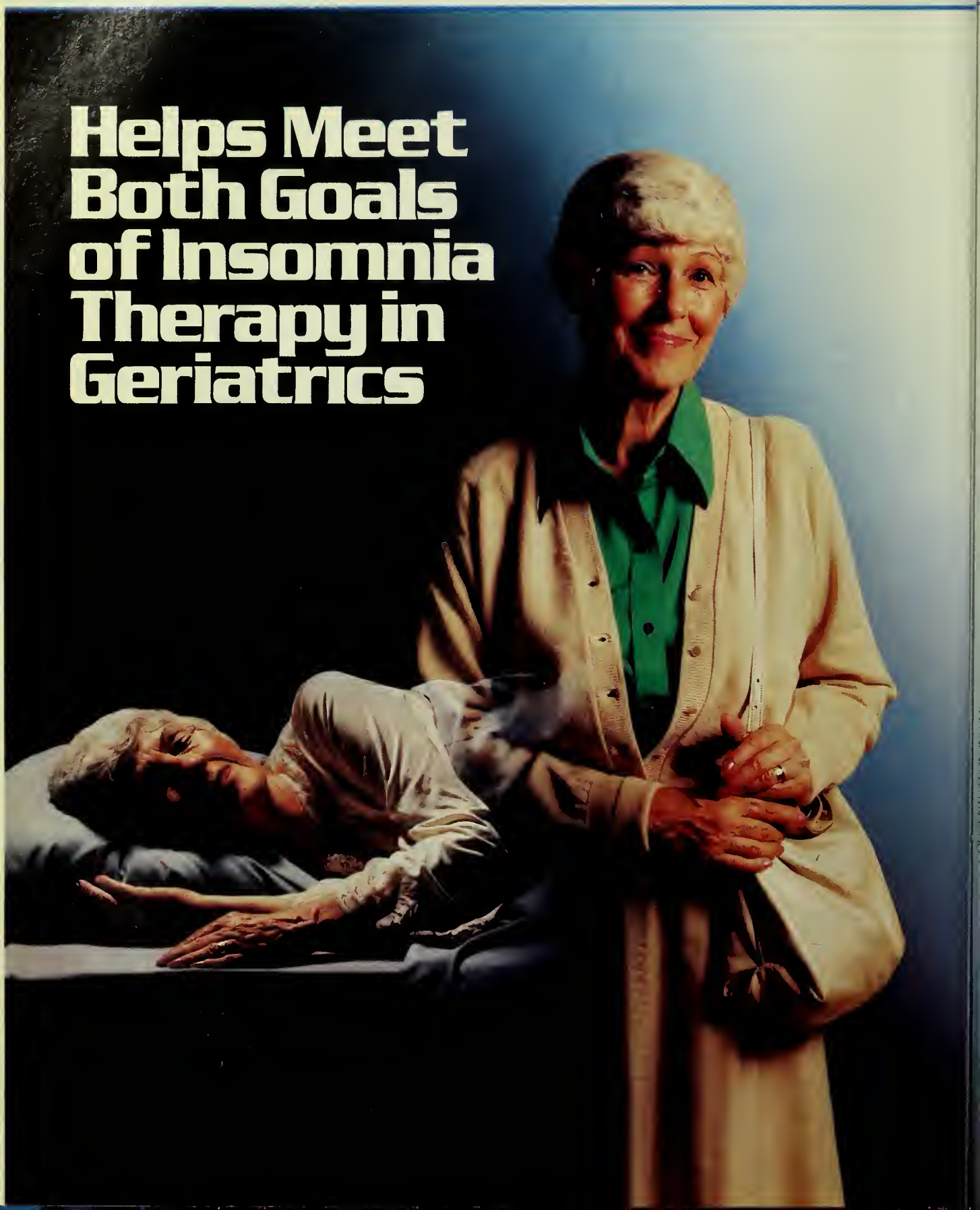
May 21-26—**Intensive Review Course in Family Medicine.** DREW at Disneyland Hotel, Anaheim. Monday-Saturday.

May 29-June 2—**11th Annual UCLA Santa Monica Hospital Medical Center Family Practice Refresher Program.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Tuesday-Saturday. 35.5 hrs. $385.

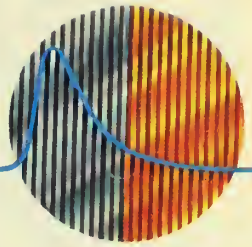
(Continued on Page 563)

Halcion® 0.25 mg Tablets

triazolam Ⓒ IV



Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion triazolam IV

0.25 mg Tablets
Initiate at 0.125 mg

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Halcion Tablets
triazolam IV

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam IV

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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Kalamazoo, Michigan 49001 USA

(Continued from Page 559)

June 1-12—**Southwestern Regional Cutaneous Flap Workshop.** Dermatology Research Foundation of California at UCLA. Friday-Saturday. 14 hrs. $495. Contact: Daniel E. Gormley, MD, 412 W. Carroll, Ste. 207, Glendora 91740.

June 5-8—**Society of Nuclear Medicine 31st Annual Meeting** at Los Angeles Convention Center. Tuesday-Friday. 36 hrs. Contact: Meetings Dept., SNM, 475 Park Ave. So., New York, NY 10016. (212) 889-0717.

June 8—**Occupational Medicine.** UCD at Beverly Garland Motor Lodge, Sacramento. Friday.

June 11-15—**Review in Clinical Chemistry.** American Society of Clinical Pathologists at Monterey. Monday-Friday. 35 hrs. Contact: Reg. Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

June 14-16—**Postgraduate Institute—Geriatrics.** CMA at Hyatt, Lake Tahoe. Thursday-Saturday.

June 17-23—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center of Long Beach at Grand Hotel, Anaheim. One week. Contact: MMCLB, 2801 Atlantic Ave., Long Beach 90801. (714) 595-3811.

June 18-20—**Aluminum-Related Disease: Features, Pathogenesis, Recognition and Treatment and Prevention.** UCLA at The Newporter, Newport Beach. Monday-Wednesday. 20 hrs. $150.

June 20-24—**Golden State Medical Association Annual Scientific Session** at Hawaiian Regent Hotel, Oahu. Wednesday-Sunday. Contact: Lillian Fortier, GMSA, P.O. Box 2151 Station A, Berkeley 94702.

June 21-23—**1st Annual Superficial Anatomy and Cutaneous Surgery for Dermatologists: 1984.** UCSD. Thursday-Saturday. 22.5 hrs. $500.

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** See Pediatrics, June 29-30.

July 7-8—**Weekend with the Masters.** UCSD and Great Teachers Foundation at Double Tree Inn, Monterey. Saturday-Sunday. 20 hrs. $325. Contact: P.O. Box 61203, DFW Airport, TX 75261. (214) 659-4590.

July 10-12—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday. 22 hrs. $300.

August 1-4—**Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday.

August 11-18—**4th Annual Fine Needle Aspiration.** UCSF. One week.

August 17-19—**Nutrition, Obesity, and Weight Control—White Water Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, P.O. Box 6009, Redding 96099.

September 1—**Medical Mycology.** UCSF. Saturday.

September 17-21—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

September 19-21—**State of the Art in the Care of Geriatric Patients: Pre-Intra-Post-Operative Management.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $325. Contact: Robin B. Jackson, Office of Cont. Ed., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

September 19-23—**Annual Scientific Program and Postgraduate Course of the Pacific Coast Fertility Society** at Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

September 20-23—**34th Annual Obesity and Associated Conditions Symposium.** American Society of Bariatric Physicians at MGM Grand Hotel, Reno. Thursday-Sunday. 17 hrs. Contact: Randall B. Lee, Exec. Dir., 4730 E. Caley Ave., Ste. 210, Englewood, CO 80111. (303) 779-4833.

ALASKA

June 8-12—**Alaska State Medical Association Annual Meeting.** Valdez Convention Center. Friday-Tuesday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 277-6891.

June 9-16—**Advances in Pulmonary Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Katmai National Park. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

IDAHO

June 23-27—**Ethics at the Edges of Life.** University of Washington School of Medicine at Elkhorn, Sun Valley. Saturday-Wednesday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

July 25-28—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, 407 W. Bannock St., P.O. Box 2668, Boise 83701.

MONTANA

October 4-6—**Montana Medical Association Annual Meeting.** Sheraton, Billings. Thursday-Saturday. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000.

(Continued on Page 658)

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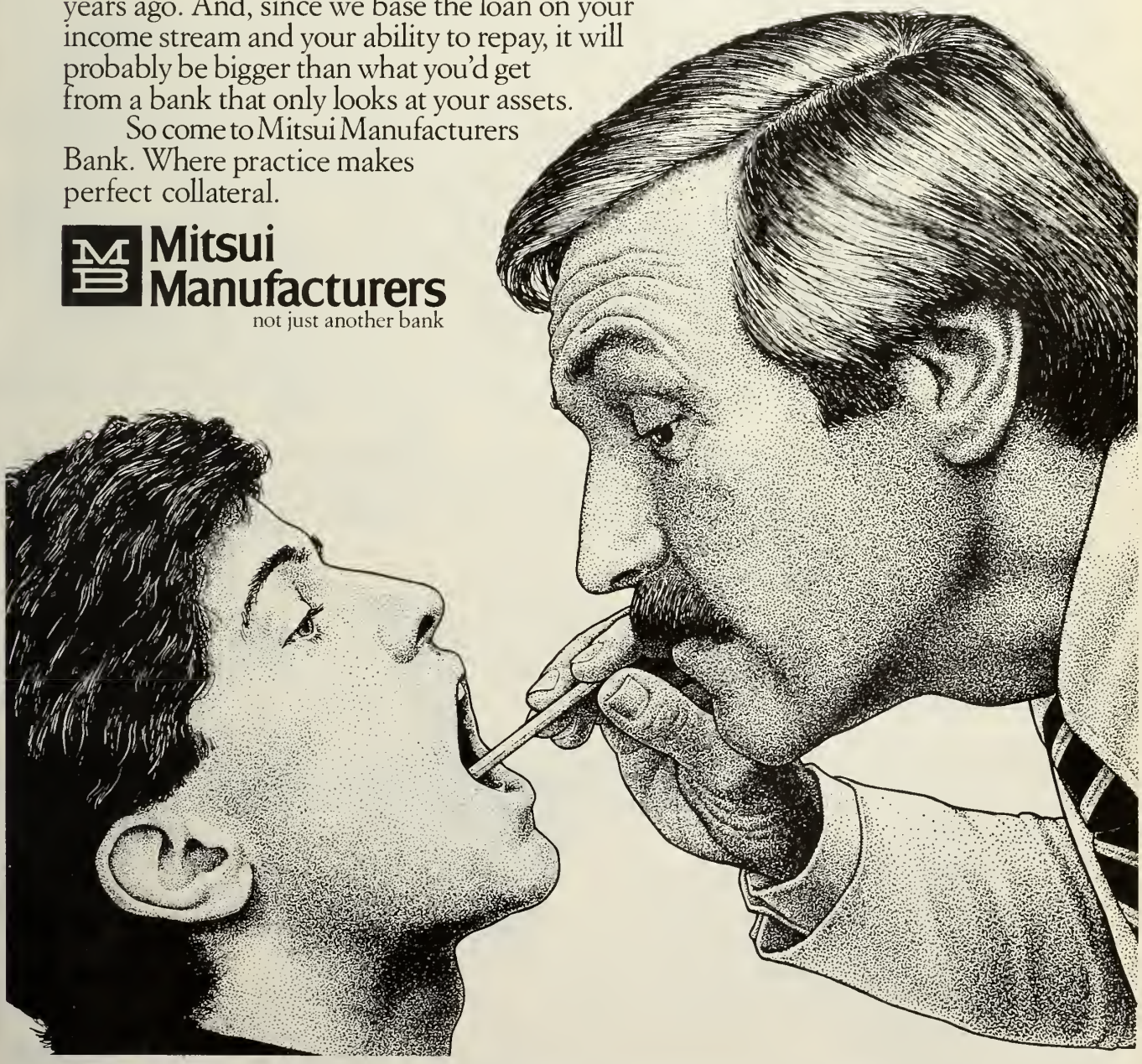

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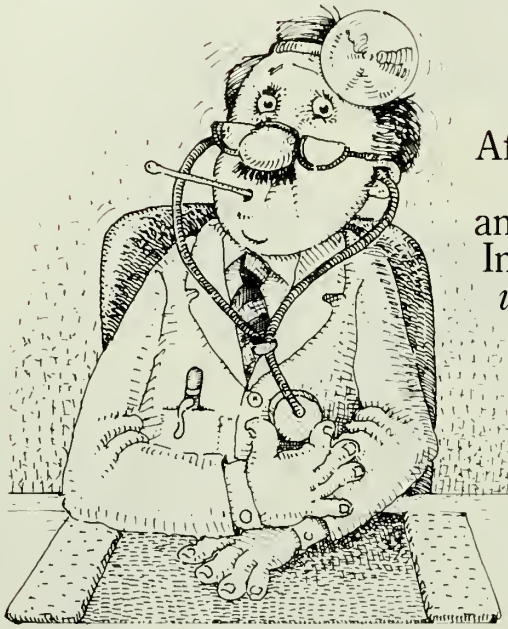

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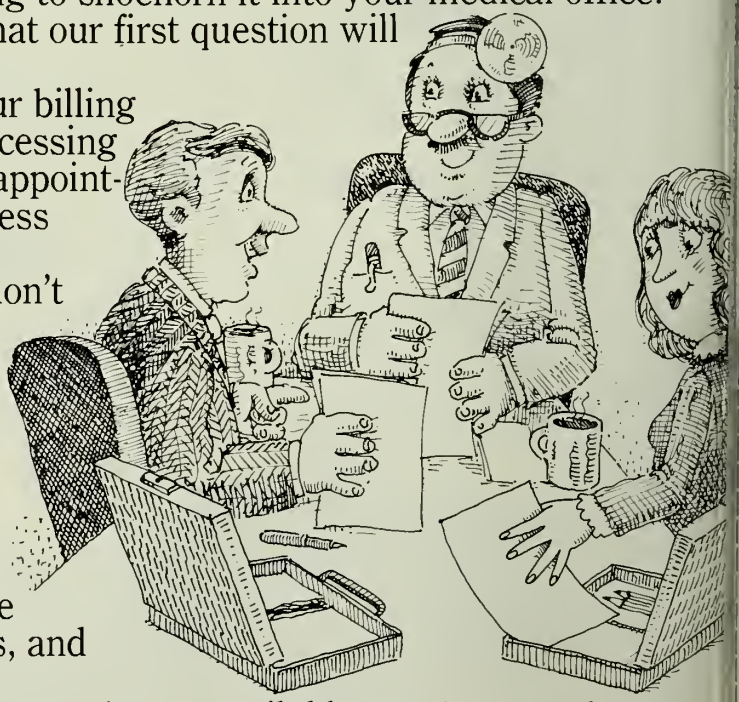
DIAGNOSES Unlike typical computer management companies, we never start by presenting a service and trying to shoehorn it into your medical office. Actually, we offer so many services that our first question will be: "What do you really need?"

Then let's sit down and list your billing needs, collection needs, insurance processing needs, management reporting needs, appointment scheduling needs, general business needs, and medical reporting needs. Together, we'll also clarify what you don't need. Only then can an efficient, cost-effective program be chosen for your medical office.



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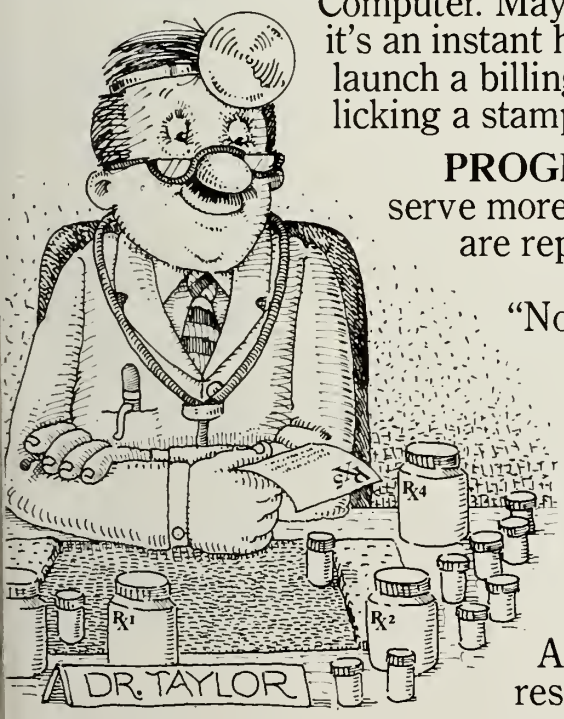

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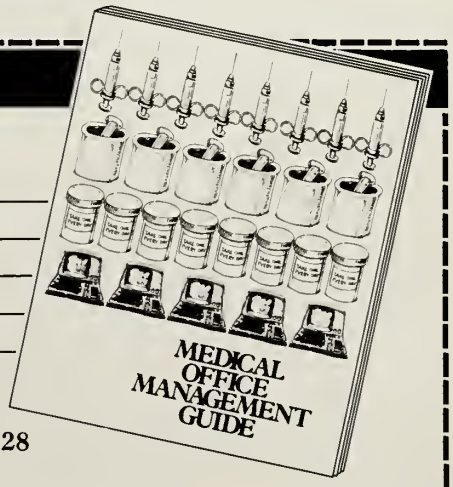

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Dyazide is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for Institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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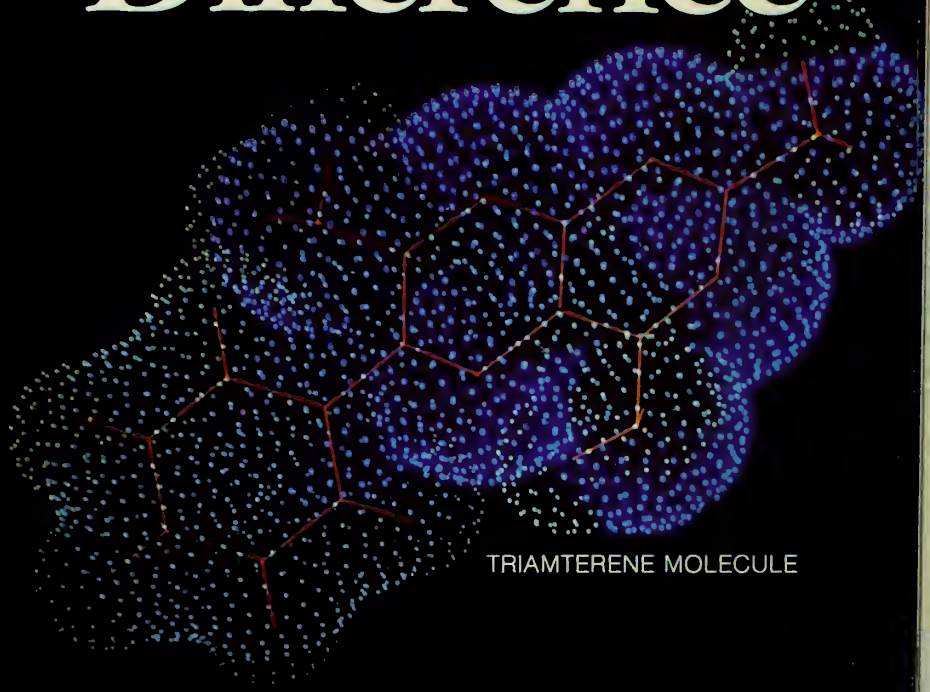

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Original Clinical Articles

Surgical Treatment of Constipation

KENNETH P. GILBERT, MD; F. GARY LEWIS, MD; RICHARD P. BILLINGHAM, MD, *and*
ERIC SANDERSON, MD,† *Seattle*

A 30-year retrospective review of 544,354 Seattle area hospital admissions yielded 25 patients who underwent surgical therapy for the relief of intractable idiopathic constipation. All patients were refractory to conventional medical treatment consisting of the daily use of laxatives, cathartics, emollients or enemas. Long-term follow-up was available for 13 of the 25 patients. All 13 patients had clinical improvement as a result of the operation. This confirms results reported by other authors. Subtotal colectomy and left hemicolectomy are the procedures generally favored.

(Gilbert KP, Lewis FG, Billingham RP, et al: Surgical treatment of constipation. West J Med 1984 Apr; 140:569-572)

The idea of surgical therapy for a functional bowel disorder has long been controversial. While constipation can nearly always be treated with diet and medication, it is often maintained that an operation is never indicated or successful. However, a patient recently seen by one of us (R.P.B.) prompted a review of area hospital experience and of the literature pertaining to surgical approaches for intractable constipation and idiopathic megacolon. We were interested in determining, first, whether or not a surgical procedure is ever appropriate in the treatment of constipation; second, if so, which patients should be considered for this drastic approach; third, what is the procedure of choice.

Patients and Methods

We retrospectively reviewed the medical records of 544,354 admissions to four Seattle-area hospitals: The Swedish Hospital Medical Center, Providence Medical Center, Northwest Hospital and Virginia Mason Medical Center. These records spanned the 30 years between 1951 and 1981. We found 25 patients who underwent a surgical procedure for constipation. The following information was obtained for each patient: age, sex, symptoms and their duration, previous operations, results of barium enema study, operations done, operative findings, histologic findings and complications. Follow-up was obtained by reviewing subsequent hospital admissions and records from physicians' offices and by telephone interviews whenever possible. Despite these efforts, several patients were unavailable for long-term follow-up.

Results

There were 20 women and 5 men, whose ages ranged from 26 years to 85 years, averaging 46 years. All patients suffered chronic constipation averaging about 18 years in duration (range 2 to 50 years). In none of these patients could a cause for the constipation be found. All patients required the daily administration of laxatives, cathartics or emollients (or all three); in addition, enemas were commonly self-administered. The average frequency of bowel movements was once a week, ranging from once every two to three days, at best, on once a month. Because of inadequate response to medical management, all of these patients sought surgical relief. In addition to chronic constipation, 23 of the 25 patients had abdominal bloating, cramping and occassionally nausea, back pain and general debility. On physical examination 68% of patients had localized or diffuse tenderness or abdominal distention. Results of preoperative barium enema studies were available for 16 of the 25 patients, primarily those patients having an operation in the more recent study period; these showed generalized or segmental dolichocolon in each case. When only a segment of the colon was dilated, this was most often the sigmoid. Five patients had a history of psychiatric disorder.

Follow-up was available on 13 of the 25 patients

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(Tables 1 and 2). The average duration of follow-up was seven years. Results were categorized as "improved" or "not improved." "Improved" was defined as meeting two criteria: the patient's subjective assessment and increased frequency of bowel movements.

These 13 patients had a total of 14 surgical procedures. One patient initially had a sigmoid resection that was unsuccessful, followed by a subtotal colectomy. Six of the patients had a subtotal colectomy, with either an ileorectal or an ileosigmoid anastomosis. All patients in this group had improvement. Five patients had a left colectomy and all of them had improvement. Three patients had a sigmoid resection, with two patients improved and one failure as previously mentioned. Those patients for whom sigmoid resection alone was satisfactory showed dilatation of only the sigmoid colon on preoperative barium enema.

Complications included one case of pelvic abscess and three of small bowel obstruction, two of which required a laparotomy. Two occurred one month after

TABLE 1.—*Type and Duration of Symptoms in 13 Patients With Intractable Idiopathic Constipation*

Patients	*Age (yrs), Sex*	*Duration of Constipation (yrs)*	*Frequency of Bowel Movements*	*Symptoms*	*Physical Findings*
1	27 ♀	27	Q 2 wks to q mo	Distention and cramping	Left-sided tenderness
2	27 ♂	27	Weekly	Nausea, vomiting, distention, pain	Distention, generalized tenderness
3	44 ♂	20	Q d to q 3 d	Pain, nausea, distention	Normal
4	50 ♀	50	Q d with enemas	None	Normal
5	55 ♀	10	Q 3 d to q 10 d	Right lower quadrant pain	Right lower quadrant tenderness
6	26 ♀	26	Weekly	Pain, distention	Rectal prolapse, distention
7	71 ♀	10	Q 3 d	Pain	Distention, generalized tenderness
8	85 ♀	5	Q 3 d to q 5 d	Distention, pain	Distention
9	44 ♀	38	Q 4 d to q 6 d	Pain, distention	Normal
10	41 ♀	41	Q 3 d to q 4 d	Cramps, distention, back pain	Tender left lower quadrant
11	62 ♀	2	Q 4 d to q 5 d	Pain, distention	Distention
12	29 ♀	26	Q 3 wks	Nausea, vomiting, cramping	Distention
13	34 ♀	30	Daily with enemas	None	Normal

TABLE 2.—*Surgical Treatment and Results in 13 Patients With Intractable Idiopathic Constipation*

Patients	*Findings of Barium Enema Study*	*Psychiatric Disorder*	*Surgical Procedure(s)*	*Complications*	*Pathologic Findings*	*Duration of Follow-up Months*	*Results*
1 ...	Dilated colon	None	Sigmoid resection; subtotal colectomy*	None	Abnormal myenteric plexus	1	Not improved; improved
2 ...	Dilated colon	Mental retardation	Subtotal colectomy	Pelvic abscess	Megacolon	12	Improved
3 ...	Dilated colon	None	Left colectomy	None	No abnormalities	290	Improved
4 ...	Redundant sigmoid	None	Left colectomy	None	No abnormalities	298	Improved
5 ...	Dilated colon	None	Subtotal colectomy	SBO	Melanosis coli	18	Improved
6 ...	Dilated colon	Anorexia nervosa	Left colectomy	None	No abnormalities	2	Improved
7 ...	Diverticula, dilated colon	Manic depression	Left colectomy	SBO	Diverticula, melanosis coli	154	Improved
8 ...	Dilated sigmoid	None	Sigmoid colectomy	None	Chronic vascular congestion	24	Improved
9 ...	Dilated left colon	Occasional depression	Subtotal colectomy	SBO	Dilated colon	8	Improved
10 ...	Dilated left colon	Neurotic	Left colectomy	None	Vascular congestion	192	Improved
11 ...	Dilated sigmoid	None	Sigmoid colectomy	None	No abnormalities	78	Improved
12 ...	Dolichocolon	None	Subtotal colectomy	None	Abnormal myenteric plexus	5	Improved
13 ...	Dilated colon	None	Subtotal colectomy	None	Abnormal myenteric plexus	2	Improved

SBO = small bowel obstruction.

*The second operation done following unsuccessful results with first procedure.

TABLE 3.—*Causes of Constipation*

Mechanical
Inadequate dietary roughage
Immobility
Fissures
Strictures
Cancer
Volvulus
Diverticulitis
Intussusception
Hernia
Dehydration
Endometriosis
Radiation proctitis
Suppression of defecatory urges
Infections
Chagas' disease
Lymphogranuloma venereum
Pharmacologic
Parasympatholytic drugs
Phenothiazines
Neurologic
Depression
Poliomyelitis
Hirschsprung's disease
Paraplegia
Psychogenic
Metabolic
Hypokalemia
Lead poisoning
Porphyria
Hypothyroidism
Functional or Idiopathic

the operation and one at 1½ years postoperatively. Routine pathologic examination in all 25 cases showed no abnormalities except for enlargement of the colon, with occasional findings of diverticulosis, melanosis coli and chronic vascular congestion. Only 1 of the 25 patients was found to have abnormal Auerbach's or myenteric plexuses by conventional microscopy. Special histologic techniques, recently developed,[1-3] were applied in the last three cases, and in all three definite severe abnormalities of Auerbach's or myenteric plexuses were found.

Comment

Constipation so severe and intractable as to require surgical intervention is distinctly uncommon. Often the precipitating factors are readily identified in a review of a patient's habits and history, such as inadequate dietary fiber intake, ingestion of constipating medicines and so forth. Regardless of cause, the great majority of cases respond satisfactorily to medical management. If the problem persists, however, and the rectum is chronically distended with feces, a patient becomes less and less aware of rectal fullness. Evacuating the rectum becomes progressively more difficult and the patient turns to the use of laxatives, cathartics, emollients or enemas (or all of these). Animal studies have shown definite histologic damage from anthraquinone laxatives,[4] and this presumably occurs in humans as well. Its motility now further impaired by such damage, the colon eventually becomes refractory to these pharmacologic or mechanical aids. In response to this over time, the colon may elongate, dilate and become flaccid. The degree of dolichocolon is usually thought to be proportional to the duration and severity of constipation.

Constipation may be due to a number of causes (see Table 3). There is now some evidence that patients with functional or idiopathic constipation may have some abnormality of bowel innervation.[1-3] As described by Michael D. Schuffler, MD (Seattle), a technique of silver staining now being developed often shows axonal fragmentation and clusters of small nuclei within ganglia that may represent some type of neuron precursor that has failed to develop into a mature neuron (oral communication, 1981). At present, however, this technique is only applicable to resected colon specimens. Currently, the diagnosis of functional constipation is most often made by exclusion.

To evaluate such a disorder, a careful history and physical examination need to be done. A barium enema and a full-thickness rectal biopsy should be done to determine the presence of ganglia. In addition, gastrointestinal motility studies may be helpful, but the role of these is currently under investigation.

The first proposed surgical therapy for constipation was lumbar sympathectomy. This resulted in little success. Dixon and Judd in 1948 reported 26 cases with two deaths and only one patient improved.[5]

Several series report results of a colon resection for constipation. The small numbers of patients and the variety of procedures done, sometimes within the same series, often preclude meaningful comparison.

In 1966 Watkins reported the cases of three patients with intractable constipation treated with subtotal colectomy.[6] All had good results.

Mahorner in 1969 reported seven cases treated with right hemicolectomy in one patient and left hemicolectomy in the other six.[7] All of these patients had successful outcomes.

In 1977 Streuli and Fartab described the cases of 28 patients who underwent subtotal colectomy.[8] All of these patients had very satisfactory results. They reported slightly better success with subtotal colectomy than with partial resection.

Another series of patients, reported in 1977 by Lane and Todd from St Mark's Hospital in London, showed resolution of constipation in seven of eight patients who had a subtotal colectomy.[9] Only one of the three patients with sigmoid resection did well. One patient who had a right hemicolectomy had only partial resolution of symptoms. Two left colectomies were carried out, with one patient showing improvement.

McCready and Beart from the Mayo Clinic in 1979 reported the cases of 23 patients who underwent a variety of surgical procedures.[10] They reported that the Swenson endorectal pull-through procedure gave satisfactory results but was associated with the highest morbidity and resulted in the one death in their series. Anterior resection resulted in a successful outcome in

six of eight patients, all of whom had dilatation confined to the rectosigmoid. For patients in whom the dilatation was more widespread, they recommended extended left colectomy or subtotal colectomy as the procedure of choice.

The most recent series, describing results in 48 patients, is reported by Belliveau and co-workers from the University of Minnesota.[11] In all, 37 patients had subtotal colectomies and follow-up was available in 29 cases. Of the 29 patients, 24 showed improvement. Eight sigmoid resections were done, with seven patients available for follow-up and six of them improved. One patient required a subsequent proctocolectomy with ileostomy and had good results. Two right hemicolectomies were carried out with success in one patient. The complication rate was significant (21%) and there was one death.

These authors suggested that this should lead one to a serious attempt to optimize medical management for at least six months, and to more carefully screen patients by physiologic testing with radiopaque markers and anorectal manometry to help rule out those patients with outlet obstruction who may better respond to myectomy or internal sphincterotomy.

Whereas almost all patients with constipation can be successfully managed with various medical regimens, there is a small group of patients with intractable constipation who are driven to seek surgical relief, and for whom surgical therapy is of benefit. It is now recommended that diagnostic evaluation of these cases should include a careful history and physical examination, a barium enema, a full-thickness rectal biopsy (to rule out congenital megacolon, or Hirschsprung's disease) and possibly gastrointestinal motility studies. When dilatation of the colon is confined to the sigmoid, limited resection can give good results, although more extensive resection may be necessary later. Subtotal or left colectomy resulted in improved bowel function in all patients. There may be a slight advantage to subtotal colectomy and generally this seems to be the procedure of choice for disease not specifically limited to the sigmoid colon.

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Indications for Vena Caval Fenestration

MARY WILKINSON GRAU, MD, and STANLEY L. SCHRIER, MD, *Stanford, California*

A retrospective study of 20 patients who underwent vena caval fenestration showed that in 50% of the patients the procedure was done for prophylaxis and in 50% it was done for therapeutic reasons. After this procedure five patients had persistent leg swelling, two had deep venous thrombosis, two had pulmonary emboli and one died of a respiratory arrest. We recommend limiting the use of vena caval fenestration to those patients who have verified pulmonary embolism while adequately anticoagulated or patients who have pulmonary embolism and a major contraindication to anticoagulation.

(Grau MW, Schrier SL: Indications for vena caval fenestration. West J Med 1984 Apr; 140:573-574)

Anticoagulation is widely accepted as the standard therapy for established venous thromboembolism. An alternative therapy is vena caval fenestration but the indications for the use of this procedure are not as clear. There is a broad range of indications for this procedure. The extremes range from prophylaxis for patients undergoing an abdominal operation to treatment of patients in whom anticoagulation has failed or who have contraindications to anticoagulation.[1,2] Before making recommendations regarding the indications for vena caval fenestration, the benefits and risks of the procedure must be assessed in the context of whether the aim is prophylaxis or therapy for established disease, and also must be compared with other modalities in these settings. This report describes the findings of a retrospective study of 20 patients who underwent vena caval fenestration.

Patients and Methods

The charts of 20 patients who underwent vena caval fenestration from 1977 to 1982 were reviewed. Cases were selected by reviewing the angiography records of the Stanford Radiology Department from 1977 through 1982 and by reviewing cases classified as vena caval fenestration by Stanford University Hospital's record department, where the retrieval system can recover cases only from 1979 through 1981. There were 13 men and 7 women ranging in age from 24 to 79 years, with a median age of 61 years. Greenfield filters were placed in 11 cases, Mobin-Uddin umbrellas were used in 5 cases, prosthetic clips were applied in 4 cases and suture plication was used in 1 case. In reviewing the indications for vena caval fenestration and the subsequent outcome of complications, cases were classified as deep venous thrombosis if there were positive findings on a venogram and pulmonary embolism if results of a pulmonary angiogram were positive. Cases in which these diagnoses were made without objective supporting studies were classified as suspected deep venous thrombosis or pulmonary embolism, respectively.

Results

Table 1 shows both the indications for vena caval fenestration and subsequent outcome, including complications. As shown in Table 1, 10 of the 20 patients had prophylactic vena caval fenestration and in the remaining 10 the interruption was intended as a therapeutic maneuver. Both groups of patients had complications. The frequency of persistent leg swelling may be underestimated because only 12 patients were available for long-term follow-up. The respiratory arrest was fatal and occurred within 90 minutes of Mobin-Uddin umbrella placement. The hemorrhage occurred after laparotomy for prosthetic clip placement and required surgical correction. The patient was not anticoagulated at the time. The two devices that migrated were Mobin-Uddin umbrellas. The first lodged in the right renal vein without further sequelae. The second lodged in the right iliac vein, resulting in acute phlegmasia cerulea dolens with arterial spasm. This patient underwent

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TABLE 1.—*Retrospective Study of 20 Patients Undergoing Vena Caval Fenestration at Stanford University School of Medicine*

Indications	*Number of Patients*	*Outcome and Complications**	*Number of Patients*
Prophylactic			
Suspected DVT or PE	5	Leg swelling	2
PE or DVT	4	Further anticoagulation	1
Recurrent PE	1	DVT	2
		Pulmonary embolism	1
		Respiratory arrest	1
Therapeutic			
Recurrent PE on anticoagulation	2	Leg swelling	3
PE with contraindication to anticoagulation	6	Migration of device	2
DVT with contraindication to anticoagulation	1	Further anticoagulation	2
Massive pulmonary embolism	1	Pulmonary embolus	1
		Hemorrhage	1

DVT = deep venous thrombosis; PE = pulmonary embolism

*Only 12 patients were available for long-term follow-up.

surgical thrombectomy with removal of the Mobin-Uddin umbrella.

Discussion

Our patients had caval fenestration for the wide variety of reasons reflected in the literature. The extremes range from prophylaxis against pulmonary embolism in patients requiring an abdominal operation to the suggestion that use be restricted to patients who have recurrent pulmonary embolism while being optimally anticoagulated. In addition to problems with the indications for caval interruption we were concerned because in a number of patients diagnosis and management were based solely on clinical findings despite a disappointing accuracy of only 50% for either pulmonary embolism or deep venous thromboembolism.[3,4]

In our group of patients persistent leg swelling and deep venous thrombosis occurred in 33% and 14%, respectively, and these values are close to the reported ranges of 18% to 50% for leg swelling and 9% to 13% for deep venous thrombosis.[2,5,6] Whereas rates of 0% to 5%[5,6] for pulmonary embolism post fenestration have been reported, 2 of our 20 patients had angiographically recorded pulmonary embolism. There were two further complications that warrant mention. Unfortunately, because an autopsy was not done on the patient who had the respiratory arrest, the cause of arrest cannot be determined. The migration of the two umbrellas is also troublesome. Migration to renal and iliac veins has been reported previously, but in no case was there development of acute phlegmasia cerulea dolens with arterial spasm.[1,7]

Recommendations

On the basis of our retrospective review and examination of the literature, we can offer several suggestions. Because of the complications and invasive nature of vena caval fenestration, it is questionable whether it is an appropriate form of prophylaxis. It is not designed to reduce the frequency of venous thrombosis. Before its use can be justified for routine prophylaxis against pulmonary embolism in a surgical patient, a controlled trial comparing it with other methods such as administering low doses of heparin, dextran or the use of calf massaging pumps is needed.

Vena caval fenestration should be seriously considered in patients who have proved pulmonary embolism while receiving therapeutic doses of anticoagulation. It also has a role in patients with pulmonary embolism who have contraindications to anticoagulation. But these contraindications must be evaluated in context. Firm contraindications include a recent neurosurgical procedure or recent major hemorrhage (hemorrhage resulting in a drop of hemoglobin of at least 2 grams per dl or hemorrhage into a closed space) or thrombocytopenia with a platelet count of less than 50,000 per μl. Relative contraindications include a recent general surgical procedure and a history of gastrointestinal bleeding. In cases with only relative contraindications, factors including stability of a patient's condition must be considered before such a major procedure is undertaken. By limiting the use of vena caval fenestration to the restricted situations described above, the possible benefits of this procedure could be increased.

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Malignant or Accelerated Hypertension

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Malignant or accelerated hypertension is a life-threatening medical emergency that is a possible complication of practically any hypertensive disorder. If not promptly treated it can cause severe, rapidly progressive target-organ damage and death. While the histopathologic features of malignant hypertension are well recognized, the pathogenesis of the associated vascular lesions and the transition from a benign to a malignant phase are unclear. With adequate control of hypertension, progression to the accelerated or malignant phase can be prevented. Moreover, promptly and effectively reducing the blood pressure during the malignant phase can prevent, minimize or even reverse serious target organ injury. Malignant hypertension, therefore, is both preventable and treatable.

(Vaziri ND: Malignant or accelerated hypertension. West J Med 1984 Apr; 140:575-582)

Malignant or accelerated hypertension is diagnosed when there are severe diastolic hypertension usually exceeding 120 to 140 mm of mercury and one or more of the following conditions:

- hypertensive retinopathy with papilledema;
- hypertensive encephalopathy;
- renal involvement;
- acute left ventricular dysfunction—that is, left ventricular failure, pulmonary edema, angina pectoris or myocardial infarction.

In addition, microangiopathic hemolysis, weight loss, anorexia, malaise, debility and fever commonly accompany this syndrome. Polydipsia also occurs with considerable frequency and may be due to either hypovolemia or a dipsogenic effect of raised angiotensin levels, or both.[1]

The term "accelerated hypertension" is often used when symptoms and signs of malignant hypertension occur without papilledema. In this communication, however, the two terms are used interchangeably.

Incidence and Prognosis

Malignant hypertension can complicate the course of practically all forms of hypertension and as such should be regarded as a phase in the course of hypertensive disorders. Successful control of hypertension, irrespective of cause, can greatly reduce or eliminate the occurrence of the malignant phase. The transition from a benign to a malignant phase in patients with essential hypertension takes an average of 7.7 years, ranging from 1 to 30 years.[2(pp134-135)] Before the advent of effective antihypertensive agents, 6% to 8% of cases of hypertension progressed to a malignant or accelerated phase; since then the incidence has declined to about 1%. In fact, occurrence of the malignant phase in patients receiving regular antihypertensive therapy is exceedingly rare. The peak incidence of the malignant phase occurs in middle-aged patients. It is more prevalent in men than in women and more common in American blacks than in whites.

With regard to prognosis, the one- and five-year survival is 20% and 0%, respectively, in untreated persons.[3] With early and vigorous treatment, however, the one- and five-year survival has increased to 85% and 60%, respectively.[4] It should be noted that the chance for survival is lower in patients who have renal insufficiency, with one- and five-year survival being 55% and 25%, respectively.[4,5]

Etiology

The single most common cause of malignant hypertension (40%) is essential hypertension, particularly when untreated or inadequately controlled. Chronic interstitial nephropathy and chronic glomerulonephritis also commonly predispose to malignant hypertension.

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Other, less prevalent, predisposing conditions include polyarteritis nodosa, unilateral renal artery stenosis, postpartum hypertension, eclampsia, radiation nephritis, congenital renal disorders, hydronephrosis, pheochromocytoma, renal thromboembolic phenomena, scleroderma, Cushing's syndrome, primary aldosteronism, renal tuberculosis and the use of estrogen and oral contraceptive agents.[6-20] Occasionally malignant hypertension occurs—primarily in young black men—when there is no preexisting hypertension or known predisposing disorders.[21]

Pathogenesis

The pathogenesis of malignant hypertension has not been fully elucidated. Several mechanisms have been proposed as possible causes of the vascular lesions in malignant hypertension and the transition from a benign to a malignant phase.

Role of Elevated Blood Pressure

Some authors believe that severe hypertension per se is responsible for the genesis of a characteristic fibrinoid arteriolar lesion in malignant hypertension.[22,23] This viewpoint is based on the following observations: (1) malignant hypertension can complicate the course of hypertensive disorders of diverse etiology, (2) vascular lesions have been shown to correlate with the severity of hypertension in humans[23] and in experimental animals,[24] (3) vascular lesions can rapidly resolve with adequate control of hypertension,[24,25] (4) when hypertension is produced in one of a pair of parabiotic rats, only the hypertensive rat will have fibrinoid arteriolar lesions[26] and (5) necrotizing arteriolitis can occur in a pulmonary vascular bed in patients who have severe pulmonary hypertension with normal arterial blood pressure.[27,28]

Role of the Renin-Angiotensin System

The possible role of the renin-angiotensin system in the genesis of vascular lesions of malignant hypertension has been suggested by the following observations: (1) plasma concentrations of renin[29] and angiotensin[30,31] are greatly elevated in almost all patients with malignant hypertension, (2) vascular lesions similar to those seen in malignant hypertension can be produced by the administration of crude kidney extract[32,33] and renin preparations in animals that have had nephrectomies[34] and (3) angiotensin infusion can produce similar lesions in experimental animals.[35,36]

It should be noted, however, that malignant hypertension and associated vascular lesions can occur in the absence of hyperreninemia. For instance, vascular lesions similar to those observed in malignant hypertension can be produced in nephrectomized animals using various pressor agents including vasopressin and catecholamines.[37-39] In addition, fibrinoid arteriolar lesions can be produced in animals by clamping a renal artery both with contralateral nephrectomy (low renin) and without contralateral nephrectomy (high renin), provided the resultant hypertension is sufficiently severe.[40-42] Moreover, Thiel and co-workers have shown that hypertensive vascular lesions in a deoxycorticosterone-induced low-renin model can be more severe than those observed in a high-renin model induced in experimental animals by clamping a renal artery.[43] Finally, a malignant phase does, rarely, occur in cases of primary hyperaldosteronism, a condition in which the renin-angiotensin system is suppressed.

Role of Disseminated Intravascular Coagulation

The common association of microangiopathic hemolysis and intravascular coagulation with malignant hypertension is well established. To date, it is not clear whether malignant hypertension is the cause or the effect of this process. It is thought that the vascular changes contribute to the occurrence of intravascular coagulation and hemolytic anemia with erythrocyte fragmentation.[44] At times, however, hemolytic anemia precedes the onset of hypertension.[45] Linton and associates have suggested that elevated blood pressure in malignant hypertension results in alteration of permeability characteristics of small arteries and accumulation of fibrinogen in the wall of these arterioles.[46] This, in turn, causes microangiopathic hemolysis and disseminated intravascular coagulation, thereby perpetuating the associated vasculopathy.

Role of a Negative Sodium Balance

The role of sodium balance in the genesis of the malignant phase of hypertension is not fully recognized. Interestingly, however, experimental malignant hypertension is associated with increased urinary sodium excretion and negative sodium balance.[47,48] The weight loss commonly seen during the acute phase of malignant hypertension may be due to this negative salt and water balance. It has been suggested that the initial loss of sodium and the resultant activation of the renin-angiotensin system may trigger the vicious cycle leading to the malignant phase and associated vascular lesions. The underlying mechanism responsible for the initial naturesis in malignant hypertension is not clear, though alteration of renal hemodynamics has been suggested.[49]

Malignant Nephrosclerosis

When uncontrolled, malignant hypertension often results in a rapidly progressive renal lesion called malignant nephrosclerosis. With prompt and effective treatment, however, renal damage can be prevented or reversed.[3,25]

The gross appearance and size of a kidney during the acute phase depend on the nature and duration of the underlying renal disease. For instance, small contracted kidneys are seen with preexisting benign nephrosclerosis, large scars with chronic pyelonephritis and normal-sized kidneys in de novo malignant nephrosclerosis. Petechial hemorrhages on the surface of the kidneys due to rupture of arterioles give the kidneys a flea-

bitten appearance. The histologic findings may be difficult to distinguish from those associated with scleroderma and adult hemolytic-uremic syndrome. These lesions consist of three major changes:

1. Proliferative Endarteritis

Proliferative endarteritis involves the interlobular arterioles and gives rise to a so-called onion-peel appearance. It is thought to be due to fibroblastic proliferation of subendothelial connective tissue, which results in severe narrowing or obliteration of arteriolar lumina. The pronounced arteriolar narrowing or obliteration in turn causes renal parenchymal ischemia and necrosis. This lesion, which can develop with great rapidity, is regarded by some to be highly specific for malignant hypertension. The thickened intima consists of mucoid material and thin concentric layers of collagen separated by elongated fibroblasts. These cells are thought to represent modified smooth muscle cells migrating from the media through disrupted internal elastic lamina. The ground substance appears to be acidic mucopolysaccharide similar to that seen in systemic sclerosis.[50] In addition, macrophages containing lipid droplets may be present in the thickened intima of the affected arterioles.

2. Necrotizing Arteriolitis

Necrotizing arteriolitis is characterized by fibrinoid necrosis of the afferent arterioles. In contrast to vasculitides, inflammatory cells are usually absent from the wall of the affected vessels. Intratubular and parenchymal hemorrhages, however, often occur due to disruption of the vessels. Because the finely granular eosinophilic substance found in these lesions shows staining properties of fibrin, it is referred to as fibrinoid. On immunofluorescence microscopy the material is reactive not only with antisera against fibrinogen but also with antisera against other plasma proteins including albumin, immunoglobulins and C3.[51] These changes are usually accompanied by cellular necrosis. Many authors consider necrotizing arteriolitis to be characteristic of malignant hypertension.

3. Necrotizing Glomerulitis

Necrotizing glomerulitis is characterized by fibrinoid necrosis and polymorphonuclear leukocyte infiltration of the glomeruli, whose afferent arterioles show necrotizing arteriolitis. In addition, other ischemic changes are often present, including shrinkage of the glomerular tuft and wrinkling of the basement membrane. These glomerular changes may progress to cellular proliferation that mimics chronic glomerulonephritis. The irregular and focal pattern of the glomerular involvement in malignant nephrosclerosis (rarely affecting more than a third of glomeruli) differentiates it from diffuse proliferative glomerulonephritis, which shows a widespread distribution. Occasionally extracapillary proliferation with crescent formation is seen.[52] Immunofluorescence microscopy usually shows the presence of plasma proteins, particularly fibrin, in the areas of fibrinoid necrosis and the intimal lesions of the involved arterioles.[2(pp146-148),53,54] Pathologic changes associated with underlying disorders, when present, are also seen. With prompt and effective control of hypertension the acute vascular and glomerular lesions usually regress with or without some residual scars.[3,5,25] Long-term follow-ups, however, have shown that in larger arteries that are unaffected, during the acute phase moderate to severe subintimal fibrous hyperplasia frequently develops.[5] The resultant ischemia can produce a later reduction of renal function. Partial recovery of renal function has been reported in some patients with severe renal failure after several days to several months of dialysis therapy and hypertension control.[55,56] Potential reversibility of renal lesions with blood pressure control has also been documented in both patients and experimental animals with malignant nephrosclerosis.[24,57] Renal arteriography usually shows abnormal intrarenal vasculature and irregularity of the walls of interlobar and interlobular arteries and a diminished and patchy appearance on a nephrogram.

Proliferative endarteritis and necrotizing arteriolitis may occur in other organs besides the kidney, such as the central nervous system, gastrointestinal tract, pancreas, liver and adrenal glands.

Clinical and laboratory manifestations of malignant nephrosclerosis consist of proteinuria, microscopic or gross hematuria,[58] cylindruria, oliguria and progressive azotemia. These urinary abnormalities and the associated hypertension with or without azotemia may mimic an acute nephritic or vasculitic process. However, hypertension tends to be less severe in those conditions, a history of preexisting hypertension is often lacking and urinary abnormalities and other related manifestations usually precede the onset of hypertension. Nevertheless, the differentiation is occasionally difficult and requires renal biopsy. Irrespective of the underlying disorder, rapid control of hypertension is indicated.

Hematologic Abnormalities

Hematologic abnormalities include changes of the coagulation and fibrinolytic systems and microangiopathic hemolysis. The associated microangiopathic hemolytic anemia may be initially masked by hemoconcentration, which frequently accompanies the acute phase of accelerated hypertension. Often a significant fall in the hematocrit is subsequently noted, representing the reversal of hemoconcentration with or without hemolysis and renal failure. The main coagulation abnormalities include thrombocytopenia, increased fibrin-degradation products and increased factor VIII and fibrinogen concentrations. In addition, increased sensitivity to urokinase and decreased euglobulin lysis time may be noted.[59] Increased erythrocyte sedimentation rate[60] and elevated serum IgG concentration are also seen.[19]

Endocrinologic Changes

As mentioned earlier, malignant hypertension is usually associated with intense stimulation of the renin-

angiotensin-aldosterone system. This is evidenced by pronounced elevation of serum levels of renin, angiotensinogen, angiotensin II and aldosterone. Intense stimulation of this system may be due either to the negative sodium and fluid balance or to pathologic changes involving the juxtaglomerular apparatus (or to both). These changes occasionally do not occur. Hypokalemia and alkalosis are often noted in cases of malignant hypertension and represent the effects of increased aldosterone levels on renal electrolyte handling. Due to intense adrenal stimulation, aldosterone overproduction and associated electrolyte abnormalities may persist long after the reversal of volume contraction and return of the renin level to or below normal limits. This condition should not be mistaken for primary hyperaldosteronism. Abnormal stimulation of the antidiuretic hormone has also been reported in both humans and animals with experimentally induced malignant hypertension.[61,62]

Hypertensive Encephalopathy

Hypertensive encephalopathy is one of the most serious manifestations of malignant or accelerated hypertension. Its clinical picture consists of a wide spectrum of neurologic aberrations that develop acutely as a result of severe hypertension.[63] The symptoms and signs vary from severe headache, nausea, vomiting, blurred vision and confusion to transient blindness, paralysis, seizures, stupor and deep coma. Occasionally focal neurologic deficits can also develop; however, they are uncommon and should suggest other central nervous system disorders. As a result of pronounced cerebral edema, fatal cerebellar herniation may occur. This event may be facilitated or induced by lumbar puncture. In most cases the cerebrospinal fluid pressure and protein concentration are raised. Neurologic features are sometimes reversed within a few days following control of hypertension, but at times recovery is slow or incomplete. Pathologic findings include arteriolar wall thickening and necrosis, cerebral edema and areas of hemorrhage.

Hypertensive encephalopathy may be clinically simulated by other neurologic disorders such as intracerebral or subarachnoid hemorrhage, thrombotic stroke or metabolic encephalopathy such as that associated with uremia. In these and other conditions associated with intracranial hypertension, retinal hemorrhage, papilledema and arterial hypertension can occur. Consequently cause or effect relationship with hypertension may be difficult to ascertain. Arterial hypertension is usually less severe with a primary intracranial pathologic condition, focal neurologic deficits are more distinct and appear earlier in the course and central nervous system manifestations generally persist despite hypertension control. Controversy exists regarding the rapidity with which the blood pressure should be lowered in patients with hypertensive encephalopathy. Some authorities regard a prompt return of the blood pressure to a normal level as safe.[64,65] Others believe, however, that rapid reduction of blood pressure may cause irreversible ischemic brain damage and recommend a less drastic approach.[66,67]

Retinopathy

Involvement of retinal arterioles leads to obliteration or rupture of these vessels, or both. This will result in the development of certain funduscopic lesions including fluffy cotton-wool exudates representing ischemic injury to the nerve fibers, flame-shaped hemorrhages due to rupture of blood vessels and papilledema associated with intracranial hypertension. The associated symptoms include blurred vision, a narrowed visual field, transient loss of vision, scotomas and the like.

Preventing Malignant Hypertension

According to the results of the Veterans Administration's cooperative study on essential hypertension, medical management of patients reduced the incidence of congestive heart failure, hypertensive retinopathy and kidney failure.[68] In this study malignant hypertension did not develop in any of the treated patients, suggesting that it is preventable. Although controlled studies of the effect of antihypertensive therapy in patients who have renal hypertension are lacking, a similar result can probably be expected.

Treatment

The diagnosis of malignant hypertension mandates immediate admission to hospital and institution of effective antihypertensive therapy. The latter should not be delayed because of diagnostic evaluations. These measures should either be deferred or conducted concurrently with the treatment.

The prompt use of potent antihypertensive drugs is the mainstay in the treatment of malignant hypertension. The immediate aim of the treatment should be to reduce the diastolic blood pressure to about 90 to 105 mm of mercury within a few hours. Caution should be exercised in patients with advanced arteriosclerosis who may fail to maintain adequate blood flow to the vital organs following a rapid fall in blood pressure. Because this can cause thrombosis or ischemic damage, particularly in the central nervous system, rapid reduction of diastolic blood pressure below 100 mm of mercury may be undesirable (see section on encephalopathy). The initial fall in tissue perfusion following blood pressure control in cases of malignant hypertension is best illustrated by the common occurrence of a transient increase in plasma creatinine and urea concentrations.

Oral medication can be initiated concurrently with, or anytime after, the initiation of emergency parenteral therapy. The dose of oral agents should be titrated to produce the desired blood pressure without the use of parenteral agents. The use of diuretics during the acute phase depends on the sodium and fluid balance. Due to the known negative sodium balance and intravascular fluid contraction during the acute phase of malignant hypertension, the use of diuretics initially is not warranted. Later, however, diuretics may be necessary as fluid retention becomes evident. In addition, diuretic

therapy can be instituted at the time of presentation in a few patients who have evidence of sodium excess and fluid overload. The argument against the initial use of diuretics in cases of malignant hypertension is strengthened by the reported successful treatment of this condition with saline infusion.[69,70] A brief discussion of the mechanisms of action, indications, contraindications, routes of administration and side effects of the drugs used in the acute phase of malignant hypertension follows.

Diazoxide

Diazoxide is a benzothiadiazine derivative that structurally resembles thiazide diuretics but lacks diuretic effect. It is a potent arteriolar smooth muscle relaxant but has no effect on the capacitant vessels and arterial baroreceptors. Consequently, its hypotensive effect is associated with tachycardia and increased cardiac output. The latter effects can lead to angina pectoris and even myocardial infarction in the presence of coronary artery insufficiency. While the exact subcellular mechanism of diazoxide's action remains uncertain, it is believed to be due to either depletion of the intracellular calcium (Ca^{++}) pool or the blockade of Ca^{++} release or Ca^{++} receptors.

When injected intravenously, diazoxide usually produces a prompt fall in blood pressure within a minute, reaching its maximum effect within two to five minutes with the effect lasting 3 to 15 hours. The conventional dose of diazoxide is 5 mg per kg of body weight in children and 300 mg in adults rapidly given intravenously. If not effective the dose can be repeated 30 minutes later.

While highly effective in rapidly lowering blood pressure, the use of a standard dose of diazoxide can be associated with serious consequences including severe hypotension, stroke, angina pectoris, myocardial infarction and even death.[71-73] Slow intravenous infusion of diazoxide has recently been shown to be effective in controlling severe hypertension.[74] In addition, small doses of diazoxide (100 to 150 mg) given intravenously (miniboluses) have been effective and relatively free of the serious complications.[75] The dose can be repeated every five minutes until the desired blood pressure is attained. Irrespective of the mode of administration, the use of diazoxide in patients with coronary artery insufficiency requires concomitant administration of a β-blocker to prevent myocardial ischemia.

In addition to the major side effects mentioned earlier, diazoxide can lead to hyperglycemia (inhibition of insulin secretion), potentiation of the coumarin effect (competition for protein binding sites), hyperuricemia, fluid retention and the arrest of labor in pregnant patients (relaxation of uterine smooth muscle). This last effect can be reversed by administering oxytocin.

Sodium Nitroprusside

Sodium nitroprusside is one of the most effective antihypertensive agents presently available. Its only route of administration is intravenous. It is a direct vasodilator that, unlike diazoxide and hydralazine, affects both arterial and venous systems. It can, therefore, reduce cardiac output and readily cause extreme hypotension. Due to the reduction of both preload and afterload, it may ameliorate the associated heart failure. The drug is available as a sterile powder, which is usually dissolved in 5% dextrose in water and slowly infused intravenously. The usual starting dose is 0.2 to 0.5 μg per kg per minute and can be increased to a maximum of 8 μg per kg per minute. The rate of infusion is determined and adjusted by careful and frequent blood pressure monitoring. Continuous blood pressure monitoring through an arterial line is highly desirable. The onset and duration of the action of nitroprusside is one and three to four minutes, respectively, with the peak effect occurring between one and two minutes. It consistently lowers the blood pressure in most patients, even those resistant to other drugs. Its use does not result in tachyphylaxis (drug resistance). When in a solution, it is inactivated upon exposure to light, so the bottle and the tubings should be covered to prevent inactivation. Prolonged use of this drug (more than 48 hours) especially at high doses can lead to thiocyanate toxicity. This is due to the generation of cyanide in tissues, which is rapidly converted to thiocyanate. When the plasma thiocyanate level exceeds 10 to 12 mg per dl, weakness, nausea, tinnitus, dizziness, hypothyroidism and even psychosis can develop. A thiocyanate toxic reaction can occur more readily in patients with renal failure due to its reduced renal excretion. Intermittent hemodialysis is effective in removing this substance and alleviating the associated symptoms. The blood thiocyanate level should be measured periodically in patients receiving nitroprusside. A reversible hypothyroidism can occur with prolonged nitroprusside treatment. Following withdrawal of nitroprusside, the thyroid function returns to normal spontaneously.

Hydralazine Hydrochloride

Hydralazine hydrochloride is a potent antihypertensive drug that causes vasodilation by direct effect on the smooth muscles of the arterioles. Reflex tachycardia, throbbing headache and a lupuslike syndrome are among its major side effects. Because of reflex tachycardia, myocardial oxygen consumption increases with this drug. Angina and myocardial infarction may develop in patients with ischemic heart disease if tachycardia is not controlled. Simultaneous use of β-blockers not only counteracts this effect, but also potentiates the antihypertensive action of hydralazine. It is, therefore, necessary to use β-blockers in conjunction with hydralazine in such patients. Intramuscular or intravenous injection of hydralazine in doses of 5 to 30 mg every four to six hours is frequently adequate for controlling malignant hypertension in most patients. In large doses hydralazine can cause agitation and anxiety, which may be confused with symptoms of hypertensive encephalopathy. If after two hours the blood pressure cannot

be controlled with parenteral hydralazine, another agent should be used.

Trimethaphan Camsylate

Trimethaphan camsylate and other ganglionic blocking agents exert their antihypertensive action by competitive inhibition of acetylcholine in sympathetic ganglia, thus preventing postsynaptic depolarization. With slow intravenous infusion, trimethaphan camsylate exerts a potent blood pressure-lowering action that is potentiated by postural effects. The need for constant monitoring of blood pressure, parasympatholytic side effects—that is, dry mouth, urinary retention, visual impairment associated with cycloplegia, tachycardia, constipation and ileus—and the development of resistance to the drug are among its major disadvantages.

Reserpine

By depleting the postganglionic catecholamine stores, reserpine and other *Rauwolfia* preparations interfere with adrenergic neurotransmission and thereby reduce peripheral vascular resistance. Reserpine can be administered intramuscularly in doses of 1.0 to 2.5 mg in a hypertensive crisis. There is usually a delay of 1½ to 2½ hours (sometimes 8 hours) in the onset of its action, which lasts about 7½ to 8 hours. A delayed and unpredictable response and various side effects (mainly nasal congestion, peptic disorders and central nervous system depression) are among the disadvantages of the use of this drug.

Clonidine Hydrochloride

Clonidine hydrochloride is a centrally acting α-agonist whose usefulness in the long-term management of hypertension is well established. Intramuscular injection of clonidine in a dose of 150 μg can produce a hypotensive response within 30 minutes that lasts four to six hours. If necessary, the dose may be repeated after 60 minutes. Unlike diazoxide and hydralazine, clonidine does not increase the heart rate and cardiac output. It is, therefore, safer in patients who have ischemic heart disease than the former agents. When given intravenously, clonidine may transiently augment the hypertension due to its weak α-agonistic property. The initial dose should therefore not be given intravenously, but this route can be used subsequently without added risk. It should be noted that clonidine has a sedative effect that can complicate the assessment of the associated encephalopathy. Oral administration of clonidine should be initiated concurrently with parenteral dosing to allow discontinuation of the latter and the maintenance of hypertension control.

The oral administration of clonidine for rapid titration of blood pressure in cases of severe hypertension has recently been advocated by several investigators.[72-78] Using rapid titration with oral clonidine, Spitalewitz and co-workers[76] were able to effectively lower the blood pressure in 20 patients with severe hypertension. They administered 0.2 mg of clonidine as the initial dose followed by 0.1 to 0.2 mg at one hour and 0.1 mg hourly thereafter as necessary (not to exceed 0.8 mg). The blood pressure fell from 212±7/134±3 mm of mercury on presentation to 151±5/104±3 mm of mercury within about two hours. The average cumulative dose producing the desired response was 0.32±0.02 mg. Most of the patients were treated in an emergency room as outpatients and only a few were admitted to hospital. The results of these studies suggest that rapid titration with oral clonidine is effective in controlling severe hypertension. This approach may be inadequate, however, in treating patients who have florid malignant hypertension; such patients should receive rapidly acting potent parenteral agents under close observation.

With the use of one of the above modalities, the blood pressure should be promptly lowered to a safe level. When possible, the use of oral agents should be initiated with the onset of parenteral therapy or shortly thereafter to allow gradual reduction and discontinuation of the parenteral drugs. Heparin and dipyridamole have been recommended by some investigators to limit the associated microangiopathic hemolysis and intravascular coagulation.[79,80] Due to their potential risks and uncertain usefulness, however, the use of anticoagulants in such patients is not recommended at this time.

Dialysis

Renal failure with associated uremia is a common complication of malignant hypertension. In the predialysis era 95% of the mortality in cases of malignant hypertension was caused by uremia. In addition to its lifesaving value, dialysis can serve as a diagnostic tool to differentiate the metabolic form from the hypertensive form of encephalopathy. Furthermore, because fluid overload associated with renal insufficiency can contribute to hypertension, fluid removal by dialysis can facilitate blood pressure control in a case of malignant hypertension.

Role of Surgery and Nephrectomy

A few patients in whom malignant hypertension is associated with surgically correctable lesions, such as with renal artery stenosis, primary hyperaldosteronism or coarctation of the aorta, will benefit from the surgical correction of the lesion.

Bilateral nephrectomy in patients who have malignant hypertension results in a dramatic reduction of the hypertension. This procedure has been used in the past for the management of certain patients with intractable malignant hypertension. With the availability of potent antihypertensive agents, however, nephrectomy no longer has a place in the treatment of this disorder. Even in the presence of irreversible renal failure, this procedure should be avoided when possible, due to the added difficulties with anemia, bone disease and fluid and electrolyte disorders associated with an anephric state.[81] Moreover, partial recovery of renal function may occur, obviating the need for dialysis in some patients months after the initiation of

dialysis.[55,56] A small subgroup of dialysis patients with severe hypertension have severe hyperreninemia, pronounced volume-independent hypertension, anorexia, weight loss and progressive deterioration of their general condition. Bilateral nephrectomy may be indicated in such patients.[82] The procedure may also be rarely indicated in the treatment and prevention of severe hypertension in renal transplant recipients.[83]

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Continuous Passive Motion for Joint Mobilization

QUESTION:

Is it considered acceptable medical practice to use continuous passive motion as a routine standard procedure in the postoperative management of stiffening conditions?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery, Orthopedics and Physical Medicine and Rehabilitation, continuous passive motion is considered established practice in the postoperative management of stiffening conditions associated with total knee or total hip replacement and muscle and joint release surgical procedures. Additional indications include intraarticular fracture operations of the knee, hip, elbow and shoulder.

Use of continuous passive motion has been shown to reduce postoperative swelling and pain, and to improve range of motion in patients who have undergone the surgical procedures noted.

Continuous passive motion is also an accepted modality of treatment for intraarticular fractures and stiffening conditions.

Medical Progress

The Heart in Diabetes

DEAN J. KEREIAKES, MD; JAMES L. NAUGHTON, MD; BRUCE BRUNDAGE, MD, *and* NELSON B. SCHILLER, MD, *San Francisco*

Since the introduction of insulin, heart disease has become a major impediment to survival in persons with diabetes mellitus. Coronary disease has increased severity and accelerated development in diabetic persons compared with an age- and sex-matched nondiabetic population. A peculiar vulnerability of women to the influence of diabetes with loss of premenopausal coronary disease protection has been found. The symptomatology of coronary events may differ and coronary care data show a higher incidence of sudden death in diabetic patients who have a myocardial infarction than in their nondiabetic counterparts. Insulin may play a role in the myocardial adjustment to an ischemic insult by enhancing glucose intake and suppressing lipolysis and ketogenesis. Carbohydrate intolerance in dogs, rhesus monkeys and humans appears associated with similar histologic and compositional changes in the myocardium. Abnormalities in diastolic ventricular function not attributable to large- or small-vessel coronary disease have been found in the diabetic subjects of each species. Studies in humans who have diabetes have assessed single pressure-volume relationships and more exacting measures of ventricular compliance are needed. Abnormalities of myocardial function in patients with diabetes have been found using echo and radionuclide techniques. Many of these findings need to be correlated with invasive data or confirmed in larger populations. Autonomic dysfunction is common in diabetic persons and may imply an associated poor prognosis. Reflex abnormalities in parasympathetic function are most prevalent and occur before sympathetic dysfunction.

(Kereiakes DJ, Naughton JL, Brundage B, et al: The heart in diabetes [Medical Progress]. West J Med 1984 Apr; 140:583-593)

Heart disease is a major cause of morbidity and mortality in diabetic patients. Its epidemiology and pathogenesis have been the subject of active investigation and controversy. A review of the topic of heart disease in diabetes is appropriate now in light of much new information. In addition to discussing coronary artery disease, the concept of a diabetic cardiomyopathy that is distinct from epicardial coronary artery disease will be substantiated with recent pathologic and hemodynamic findings. The role of insulin in myocardial metabolism will be elaborated and the manifestations of autonomic reflex dysfunction reviewed. No attempt will be made to elucidate the pathogenesis of atherosclerosis per se, as this has been the subject of other recent reviews.[1-3] As a single review cannot possibly deal completely with all aspects of heart disease in patients with diabetes mellitus, readers are referred to other literature on the subject as well.[4-7]

Coronary Artery Disease

In the preinsulin era, coronary artery disease was an uncommon cause of death in patients with diabetes mellitus, being responsible for 2% to 9.9% of all reported deaths.[8,9] The advent of insulin brought dramatic improvement in survival for diabetic persons and major shifts in the causes of death. Metabolic coma and infection no longer loomed as the primary obstacles to survival but were succeeded by cardiovascu-

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ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
FFA = free fatty acid
PAS = periodic acid-Schiff

lar and renal disease (Figures 1 and 2). Subsequent analyses of diabetic mortality show that despite the introduction of antibiotics and improvement in medical and surgical care, little if any improvement in survival has occurred since the advent of widespread insulin use in the 1930s.[10-13] Survival curves for diabetic cohorts established in 1939, 1949 and 1959 were not significantly different. From this pooled cohort data (Figure 3), we note that patients with an onset of diabetes before age 21 years can expect virtually no excess mortality compared with their nondiabetic counterparts for a period of 15 years. This is followed by 1.0% to 1.5% excess mortality per year, with about 75% surviving 30 years of their disease. More than half of these deaths are attributable to coronary artery disease, which has a greater impact on younger age groups when compared with deaths in nondiabetic persons.[12,14-18]

Early pathologic studies of the coronary arteries in diabetic persons purporting to show a 1.6- to 6.6-fold increment in coronary artery narrowing, occlusion or myocardial infarction were frequently flawed in design and by the lack of a standardized objective method for determining the severity of lesions.[19-29] Findings of recent quantitative studies of arterial wall changes in diabetic and nondiabetic persons suggest an increased extent and severity of disease in persons with diabetes that is otherwise indistinguishable from that in nondiabetic persons.[30-36] This difference appears most pronounced in younger age groups and is exaggerated by the presence of coexistent risk factors, especially hypertension. When previous necropsy studies are analyzed for the presence of disease (coronary narrowing, occlusion, infarction) in patients who died before age 41, diabetic persons incur a 7-fold to 15-fold excess compared with young nondiabetic persons.[22,25,26,29] This excess is greater than that obtained (twofold) when all ages are included in analysis. Despite limitations to the study of necropsy populations, the data suggest accelerated development of atherosclerotic cardiovascular disease in diabetic persons compared with sex- and age-matched nondiabetic persons.

Population studies have established diabetes as an independent risk factor for the development of cardiovascular disease including coronary artery disease.[37-44]

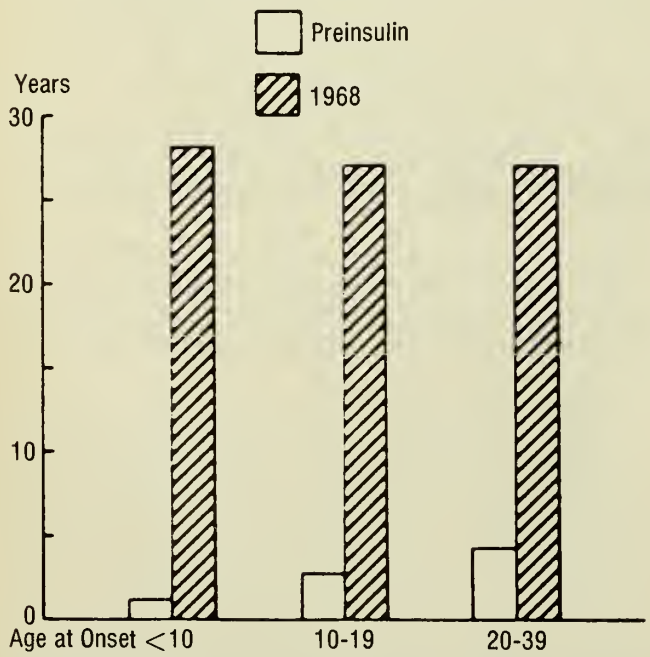

Figure 1.—Average duration of life after the onset of diabetes in the preinsulin and postinsulin eras (experience of the Joslin Clinic, Boston; from Christlieb[12]).

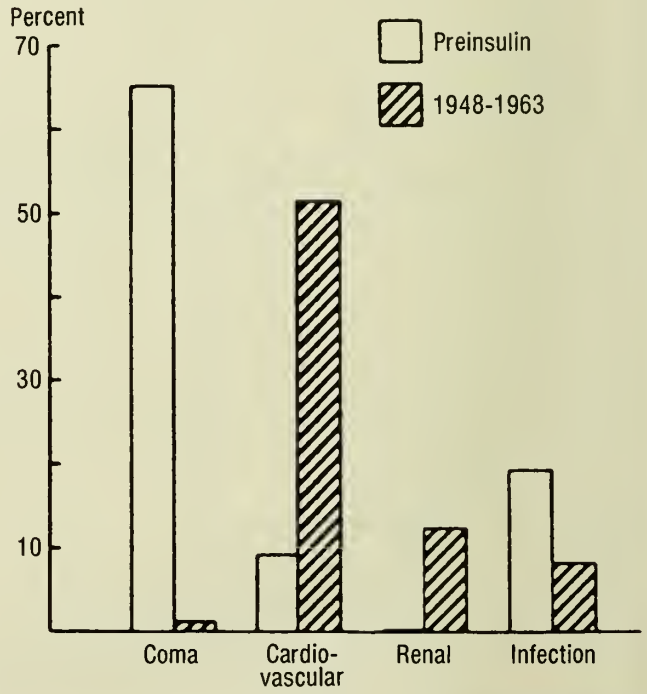

Figure 2.—Major causes of death in diabetic patients in the preinsulin and postinsulin eras (from Christlieb[12]).

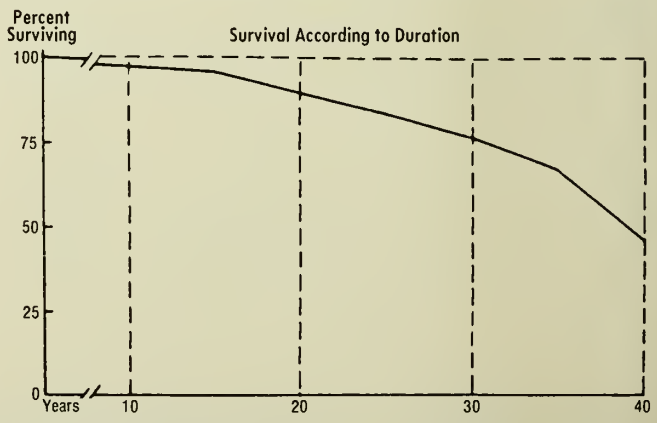

Figure 3.—Pooled survival curve for three juvenile diabetic cohorts, 1939, 1949 and 1959 (N = 285). (From Christlieb.[12])

The relative impact of diabetes as a risk factor varies with the type of cardiovascular disease, being greatest for intermittent claudication and congestive heart failure and least for coronary artery disease (which is nevertheless the major sequela on an absolute scale).[45] Several studies have shown a peculiar vulnerability of women to the influence of diabetes, even after controlling for low high-density-lipoprotein-cholesterol fraction and obesity.[38,45,46] Women who have diabetes lose premenopausal protection from coronary artery disease and, compared with nondiabetic women, have a threefold increment in death from cardiovascular disease after adjusting for other risk factors. There is an increased risk for clinical congestive heart failure developing that is greatest in diabetic women and in all patients treated with insulin.[47] This twofold to fivefold excess risk appears independent of other atherogenic risk factors or prior coronary disease status. This finding has led investigators to propose that a form of cardiomyopathy is associated with diabetes as a result of microangiopathy or abnormal metabolism, a point that will be discussed later.

Recently researchers have suggested that hyperinsulinism (endogenous or exogenous) is a factor promoting atherogenesis by stimulating proliferation of arterial smooth muscle cells, incorporating carbohydrate precursors into arterial lipid deposits and inhibiting lipid breakdown in the arterial wall.[3,48,49] Exogenous insulin, as a foreign protein and component of antigen-antibody complexes, may mediate endothelial injury and promote atherosclerosis by an immunologic mechanism.[50] Further studies in these areas may have a direct bearing on diabetic management in the future.

It has long been thought that the symptomatology and prognosis of coronary events in patients with diabetes may differ from those in nondiabetic persons. Early studies suggested that 30% of myocardial infarctions in patients with diabetes occurred without chest pain.[51-53] Analysis of infarctions diagnosed on biennial electrocardiograms in the Framingham study showed unrecognized or "silent" infarction to be almost twice as common in diabetic persons. This trend, which did not reach statistical significance, was not altered by patient age or electrocardiographically determined infarct location.[54,55] More recent data[56] show that painless infarction does indeed occur in persons with diabetes but in a smaller percentage of cases, ranging from 2.8% in patients with acute infarction[57] to a 22% prevalence of transmural scar at necropsy in patients with diabetes without a history of clinical or electrocardiographic coronary artery disease.[34] Bias in patient selection makes it impossible to determine the exact frequency of occurrence. It is important to stress that chest pain does occur in the great majority of diabetic patients who have infarction. Cases with atypical or absent chest pain frequently present with heart failure, uncontrolled diabetes, vomiting, systemic thromboembolism or vascular collapse. These presentations should suggest coexistent myocardial infarction.

Once infarction has occurred, diabetic patients do not fare as well as those who do not have this disease. Most studies in support of this premise were done before the advent of coronary care units and modern coronary care and, until now, no analysis of the cumulative coronary care unit experience had been made.[58-64] There are nine studies in the coronary care unit era that evaluate sudden death in diabetic patients.[57,65-72] At hospital discharge at an average of three to four weeks, the mortality for diabetic persons is 31% ± 2.4% compared wih 19.9% ±2.0% in nondiabetic persons (Table 1) ($P<.01$). It is more difficult, however, to explain this excess mortality from the data given. Further analysis indicates that certain complications of infarction are only 5% to 6% more frequent in the diabetic patients (Table 2). When mortality is analyzed by mode of diabetic therapy in the 706 patients from whom this information is available (Table 3), the insulin and oral hypoglycemic groups each have 33% mortality rates compared with 18% in the diet-controlled group. In each study where comparison is made of mortality by sex of the patients, women fare

TABLE 1.—*Nine Studies of Mortality in the Coronary Care Unit Era*

Reference	*Diabetic Persons Number (Percent)*	*Nondiabetic Persons Number (Percent)*
McGuire and Kroll, 1972[65]	25/54 (46)	66/341 (19)
Henning, 1976[66]	86/240 (36)	318/1,273 (25)
Soler et al, 1974[69]	94/285 (33)	..... (18)
Kvetny, 1976[67]	11/37 (30)	168/560 (30)
Harrower and Clarke, 1976[68]	24/94 (26)	661/3,481 (19)
Lichstein et al, 1976[70]	64/265 (24)	.....
Tansey et al, 1977[71]	25/89 (28)	110/793 (14)
Maempel, 1978[57]	60/289 (21)	94/656 (14)
Czyżyk et al, 1980[72]	56/154 (36)	29/154 (19)
	445/1,507 (30) (31% ±2.4%)	1,446/7,258 (20) (19.9% ±2.0%)

$P = <.01$ by Mann-Whitney U-test, Wilcoxon sign rank test.

TABLE 2.—*Cumulative Occurrence of Complications During Acute Infarction in Diabetic and Nondiabetic Persons**

	Diabetic Persons Number (Percent)	*Nondiabetic Persons Number (Percent)*
Bundle branch block	71/365 (19)	251/1,774 (14)
CHF-pulmonary edema	201/753 (27)	359/1,603 (22)
Shock	84/602 (14)	117/1,449 (8)
VT-VF	114/1,262 (9)	516/8,354 (6)

CHF = congestive heart failure,
VT-VF = primary ventricular tachycardia or fibrillation.

*From the nine studies referred to in Table 1, 1972 through 1980.

TABLE 3.—*Mortality by Mode of Therapy in 706 Patients**

Treatment	*Number*	*Percent*
Insulin	72/218	33
OHG	123/371	33
Diet	21/117	18

OHG = oral hypoglycemic agent

*From the nine studies referred to in Table 1, 1972 through 1980.

worse than men with an overall 1.4-fold higher mortality. In summary, data from the coronary care unit era show a statistically significant increase in the incidence of early death due to myocardial infarction in diabetic persons. This excess mortality may not be adequately explained by an increased incidence of acute complications. Death rates appear proportional to the severity of carbohydrate intolerance based on mode of therapy, and diabetic women have a higher relative mortality than their male counterparts. Recent findings suggest the incidence of persistently positive technetium Tc 99m pyrophosphate scans following infarction is increased in diabetic patients and is associated with major cardiac complications and death.[73] This finding, if confirmed, may aid in the identification of high risk patients during follow-up.

It has been suggested that an infrequent but severe complication of infarction, left ventricular free wall rupture, may have an increased incidence in diabetic patients. Analysis of the ten studies that note the diabetic status of the patients shows a 2.7-fold more frequent occurrence in diabetic patients dying of infarction.[19,26,34,57,72,74-78] It is not possible to assess from these studies the influence of sustained hypertension during infarction or the relatively greater percentage of women among the diabetic population. Both factors are more prevalent in patients with diabetes who have infarction and are independently incriminated in myocardial rupture. Better controlled data are needed to establish this association.

A problem that may complicate the treatment of myocardial infarction in a patient with diabetes is the development of excess extravascular lung water in the face of normal or mildly elevated ventricular filling pressures. Long-term diabetes is associated with a generalized alteration in capillary permeability[79-81] that, when coupled with low plasma colloid osmotic pressure from chronic disease, metabolic imbalance or vigorous crystalloid resuscitation, may result in extravascular fluid extravasation despite normal or near-normal hydrostatic pressures. Abnormalities in pulmonary gas exchange due to this mechanism have been described in diabetic patients.[82] If volume resuscitation is necessary in a person with long-term diabetes, the clinician should be cognizant of the colloid osmotic pressure measured directly or calculated from protein concentrations in the plasma.[83,84] Measurement of ventricular filling pressures may not be adequate in these patients and more valuable information can be obtained from the difference between colloid osmotic pressure and pulmonary capillary wedge, sometimes referred to as Starling's gradient.[85-88] It is important to remember that control of hyperglycemia with insulin and the attendant decline in intravascular fluid volume may alleviate congestive failure, particularly in patients who have impaired renal function.[89]

Insulin and Myocardial Metabolism

A relative or absolute lack of insulin may be detrimental to the metabolic adjustment of myocardium to an ischemic insult. The preferred energy substrates of the heart are glucose and long-chain fatty acids. Fatty acid oxidation prevails under aerobic conditions and accounts for 60% to 80% of the heart's energy production.[90,91]

Myocardial uptake of free fatty acids (FFA) is a function of chain length and circulating FFA-albumin molar ratio. Glucose uptake in the heart is enhanced by mechanical work, insulin and decreased tissue oxygen delivery, and is inhibited by raised circulating levels of FFA, products of fatty acid oxidation and ketones.[90,92,93] Anaerobic metabolism of glucose becomes the major source of energy for the myocardium when oxygen delivery falls to less than 20% of normal. Insulin deficiency may then impair glucose uptake in ischemic myocardium and facilitate lipolysis, thereby increasing circulating FFA and ketone levels. Elevation of catecholamine levels, described in either myocardial infarction or uncontrolled diabetes,[94,95] can increase myocardial oxygen consumption directly through β-adrenergic stimulation and indirectly by enhancing lipolysis and myocardial uptake of FFA.[96,97] Because oxidation of FFA by the myocardium requires 11% more oxygen per carbon unit than glucose, it "costs more" to use this substrate.[98-100] In addition to requiring more oxygen for catabolism, fatty acids can be toxic in an ischemic myocardium via intracellular accumulation of an acyl derivative of coenzyme A, acylcarnitine, lysophospholipids and triglycerides.[101-104] α-Adrenergic stimulation from catecholamines will further suppress whatever insulin secretory reserve is present in a diabetic patient, thereby perpetuating a vicious circle. Although these considerations are largely theoretic, increased circulating FFA can depress cardiac function and increase myocardial injury in an ischemic animal heart.[105]

Clinically, a relationship has been proposed between serum FFA levels, cardiac arrhythmias and death after myocardial infarction.[106-108] These observations have formed the basis for using infusions of glucose, insulin and potassium to enhance anaerobic glycolysis and suppress FFA metabolism during myocardial infarction. The effect of glucose, insulin and potassium is reflected by the degree of suppression of circulating FFA. In humans with myocardial infarction, glucose, insulin and potassium have been reported to suppress arrhythmias, improve ventricular function and increase survival. Decreased infarct size is described in experimental models.[109-111]

Insulin deficiency in diabetic rats has been associated with depression of calcium binding and uptake in isolated sarcoplasmic reticulum fractions and depression of contractile protein enzymatic activity (myosin and actomyosin adenosine triphosphatase [ATPase]).[112-115] Isolated abnormalities in papillary muscle function in diabetic rats have been reversed by insulin treatment, with return of contractile protein enzymatic activity to normal.[116] What relevance these findings will have to abnormalities in myocardial contractile function and ventricular relaxation in diabetic persons is unknown.

They serve to illustrate other potential mechanisms by which insulin may influence myocardial pump function.

Pathology of the Heart

Data cited previously support the concept of accelerated development of extramural coronary artery disease in patients with diabetes. The morphology of the coronary arterial lesions and their distribution appear similar in diabetic and nondiabetic persons studied at necropsy. The findings of recent clinical studies do not support the contention that patients with diabetes have more severe distal coronary artery narrowing, making them less likely candidates for coronary bypass operation.[117-122]

Various abnormalities of the intramural coronaries have been noted in diabetic patients, none of which are entirely specific.[123-129] Increased perivascular fibrous tissue, proliferation of medial muscle cells, intimal hyaline deposits and endothelial cell proliferation have been reported to occur. Periodic acid-Schiff (PAS) staining has been noted to involve the endothelial and medial areas. Most controversial are the intimal-endothelial proliferative lesions, felt by some observers to be occlusive in nature and responsible for myocardial ischemia, fibrosis and hypertrophy.[124-131] There is little evidence that these lesions, occasionally found in nondiabetic persons, represent significant occlusive lesions histologically[33] or functionally.[132] Abnormalities of diabetic myocardial capillaries include capillary basement membrane thickening,[133,134] PAS staining and saccular capillary microaneurysms.[135] Although the composition of cardiac basement membrane has not been analyzed, glomerular basement membranes in diabetic patients have been shown to contain low levels of cystine and sialic acid residues.[136,137] The influence of basement membrane thickening on oxygen diffusion and nutrient or waste fluxes is at present unknown.

The myocardium of diabetic persons has shown PAS staining preponderantly around small intramyocardial vessels and in the interstitium between muscle fibers.[132,138-140] An increase in collagen content in these areas has been shown. Areas of myocardial fibrosis and gross scar have been found even in the absence of occlusive coronary disease.[141] Histochemical analysis of human diabetic myocardium has shown a significant increment in triglyceride and cholesterol,[132,140,141] similar to changes noted in diabetic dogs and rhesus monkeys.[142-145] Changes found in diabetic animals but not yet in humans include increased hydroxyproline concentrations as a measure of collagen content[143] and preferential incorporation of C_{14}-oleic acid into triglyceride instead of phospholipid.[142] Cholesterol increments are in both free and esterified fractions and have not been further characterized.[141] The excess collagen is predominantly of the insoluble fraction, which suggests that it accumulates due to decreased degradation or increased cross linking (or both).[146] Studies measuring the incorporation of ^{3}H-hydroxyproline into myocardial collagen have shown normal rates of synthesis in diabetic animals.[144] Recent data suggest that glycosylated collagen may be less susceptible to degradation by specific collagenase enzymes.[147]

In summary, these studies have established a pattern of abnormalities present in dogs, rhesus monkeys and humans that includes increased PAS staining with increased collagen, triglyceride and cholesterol content. Nonenzymatic glycosylation of myocardial collagen may occur as shown in aortic and skin collagen.[148,149] Nonenzymatic glycosylation may alter normal collagen degradative processes causing increments in the insoluble fraction. The degree of nonenzymatic protein glycosylation is proportional to ambient glucose concentration.[150]

Noninvasive Assessment

Echocardiography has been used to assess abnormalities in systolic and diastolic function, usually preclinical in nature, in diabetic patients. Abnormalities of diastolic function are most prevalent and more likely to be present in patients who have evidence of retinopathy.[151-159] Diastolic abnormalities include delayed mitral valve opening in relation to either aortic valve closure or minimal left ventricular dimension (prolonged isovolumetric relaxation time) and incoordinate relaxation with loss of the normal diastolic relationship of the left ventricular free wall and mitral valve movement.[154-157] Left ventricular hypertrophy, when present, is associated with hypertension.[156] Abnormalities of systolic function include a prolonged preejection period and preejection period index (corrected for heart rate), a shortened left ventricular ejection time and, most significantly, an increase in the ratio of the preejection period to the left ventricular ejection time. This ratio has shown inverse correlation with the angiographically determined ejection fraction in healthy persons.[158] Reports of correction of these systolic function abnormalities with better control of diabetes have appeared, but further confirmation is awaited.[153] Whether noninvasive modalities can accurately detect abnormalities in diastolic ventricular function remains to be defined.[159-161]

Noninvasive studies have been used to assess the prevalence of asymptomatic coronary artery disease in patients with diabetes. A higher incidence of resting thallium defects has been found in a small number of asymptomatic diabetic men than in nondiabetic men.[162] In a more recent study, abnormalities in exercise tolerance and thallium scintigraphic testing were uncommon in 124 asymptomatic persons with juvenile-onset diabetes with a mean duration of disease of 23 years.[163] No conclusions can be drawn from these preliminary studies and more data are needed to establish a role for noninvasive screening of asymptomatic diabetic persons for coronary artery disease.

Diabetic Cardiomyopathy

There is accumulating clinical and experimental evidence that a disorder of heart muscle, independent of atherosclerotic coronary artery disease, occurs in diabetic persons.[132,139-145,164-166] Patients in the Framingham

study who had diabetes had an exaggerated risk of clinical congestive heart failure developing compared with their nondiabetic counterparts.[45,47] This excess risk persisted after other atherogenic risk factors and prior coronary disease status were considered, suggesting that factors other than coronary artery disease may be important.

The question of a primary myocardial abnormality in diabetes has been studied by Regan and co-workers, who first showed abnormalities in dogs.[142] Mild non-insulin-requiring diabetes was produced in young adult dogs by administering three doses of alloxan intravenously at monthly intervals. The dogs had reduced clearance of infused glucose, low insulin-glucose ratios and diminished pancreatic content of insulin at termination of the experiment. Another group of dogs received alloxan and had the pancreatic effects inhibited so that any direct effect of alloxan on the heart could be assessed. These dogs and a third control group all had normal carbohydrate tolerance. After 11 months, characterization of left ventricular function was accomplished by acute volume expansion with saline and acute afterload elevation with angiotensin. Volume expansion resulted in a twofold greater end-diastolic-pressure increment in the diabetic dogs compared with controls. Increased afterload resulted in a significant rise in end-diastolic volume and stroke work in normal dogs, but diabetic dogs had no significant end-diastolic-volume increment and a depressed stroke-work response. Similar abnormalities were found in dogs with spontaneously occurring diabetes but not in dogs in which the pancreatic effects of alloxan were inhibited. Myocardial hypertrophy was absent and indices of systolic ventricular function were normal in all groups of dogs. These results suggest decreased ventricular compliance in the diabetic dogs in the absence of obstructive coronary artery lesions. The myocardium of the diabetic dogs contained significant increments in glycoprotein, collagen, triglyceride and cholesterol.

Following 18 months of alloxan-induced diabetes in rhesus monkeys, similar abnormalities in diastolic ventricular function were found.[144] Volume expansion resulted in excessive increments in the left ventricular end-diastolic pressure and a subnormal stroke-work response in the diabetic animals. Myocardial hypertrophy and obstructive coronary artery lesions were absent and evaluation for microvascular ischemia by rapid pacing showed no abnormal lactate production or alteration of coronary flow. Abnormal compliance in the monkey ventricle was associated with the same histochemical changes noted in dogs.

To evaluate diabetes in humans, coronary angiography and left ventricular function studies were done in a group of 17 persons with adult-onset diabetes who had symptoms largely of dyspnea or chest discomfort.[132] In all, 12 patients had no significant extramural coronary disease and no evidence of microvascular ischemia as reflected by normal coefficients for lactate extraction after pacing-induced tachycardia. In the eight patients who had no signs or symptoms of congestive heart failure, ejection fraction and mean rate of fiber shortening were within normal limits. Left ventricular end-diastolic pressure-volume ratios were significantly higher in diabetic patients than in nondiabetic controls. Angiotensin-induced afterload increments resulted in a significantly greater rise in filling pressure in the diabetic persons and a subnormal stroke-work response. Two patients had left ventricular biopsy in which the specimen showed interstitial collagen deposition. Postmortem studies were done in another group of 11 persons with uncomplicated diabetes, nine of whom were without significant coronary disease. Comparison was made with five nondiabetic persons of similar age. Histologic evaluation showed more PAS positivity in the diabetic persons along with collagen accumulation and areas of fibrosis. Chemical analysis showed increased cholesterol and triglyceride content compared with controls. In summary, an abnormality of diastolic function probably reflecting decreased compliance was found in dogs, rhesus monkeys and humans. Similar histochemical changes were found in each species.

Although in these studies only single pressure-volume relationships were evaluated in a small number of patients, the data suggest reduced ventricular compliance in the absence of significant coronary artery disease. We are attempting to evaluate pressure-volume curves in similar patients for more exact information on ventricular compliance. We have no estimates of how frequently abnormalities in compliance can be found in the absence of coronary artery disease. Although the number of cases is small, two points deserve emphasis. Asymptomatic diabetic persons are rarely catheterized and, without pressure-volume curves, less severe abnormalities of compliance may go undetected. Most patients with diabetes who have symptoms that bring them to catheterization have significant coronary atherosclerosis. In many of these cases, a primary myocardial abnormality may coexist with coronary artery disease and this combination may be responsible for the worse prognosis of diabetic persons who incur an ischemic event. On the other hand, cases of congestive heart failure in diabetic persons can no longer all be ascribed solely to coronary artery disease.

Studies evaluating isolated papillary muscle function in rats made severely diabetic by the administration of streptozocin have shown delayed onset of relaxation, slowed rate of relaxation and depression of shortening velocity.[115,116] Following six to ten weeks of diabetes, insulin treatment for four weeks resulted in complete return of these abnormalities to normal.[116] The contractile activity of protein enzymes (myosin ATPase; actomyosin ATPase) was depressed during the diabetic state and returned to normal with insulin treatment. Other studies in diabetic rats have shown decreased calcium binding and uptake in isolated sarcoplasmic reticulum fractions.[112]

Many of the structural and functional alterations of the heart in diabetes have been illustrated. Much less information exists concerning the reversibility of these

changes with insulin or other hypoglycemic agents. There have been no invasive hemodynamic assessments of therapy in diabetic persons. Interpretation of the echocardiographic results showing improvement in noninvasive indicators with hypoglycemic therapy is impossible at this time and further studies are needed. Treatment in diabetic dogs has been associated with both lack of resolution[143] and partial but incomplete resolution of diastolic abnormalities measured invasively.[167] In one study, oral hypoglycemics resulted in exacerbation of compliance abnormalities.[168] Reversibility of abnormal function in rats has been summarized above.

Autonomic Reflex Dysfunction

Abnormalities in cardiovascular autonomic reflexes were demonstrable in 20% of an unselected population of diabetic persons.[169] A progression of abnormalities occurs first, affecting the parasympathetic system, followed by sympathetic dysfunction.[169-180] The reverse sequence has not been described. Complaints of impotence or diarrhea alone are not reliable markers for associated cardiovascular reflex abnormalities.[169] Autonomic dysfunction may be present at the time of diagnosis of diabetes and can occur in the absence of clinical peripheral neuropathy. However, patients with abnormal autonomic reflexes have more frequent and more severe abnormalities in peripheral nerve conduction studies. Autonomic reflex dysfunction has an associated poor prognosis for a patient,[169-171] but its definition through multivariate analysis as an independent prognostic variable has not been established. Parasympathetic dysfunction is reflected by a resting tachycardia of 90 to 100 beats per minute, which is unresponsive to reflex maneuvers. Rates up to 130 have been described[181] and the rate may actually slow and become unresponsive to reflex or pharmacologic manipulation ("fixed") with subsequent sympathetic damage.[182]

Orthostatic hypotension from depletion of peripheral presynaptic norepinephrine is well described and has recently been reviewed.[183-185] This hypoadrenergic variant of postural hypotension in diabetic persons is associated with low supine norepinephrine levels, a blunted norepinephrine response to standing or tyramine administration and an exaggerated blood pressure response to infused norepinephrine.[186] A hyperadrenergic variant of postural hypotension in diabetic persons associated with raised norepinephrine levels has also been described by Cryer and associates.[187] Although originally thought to be due to vascular resistance to endogenous norepinephrine, further studies have shown intravascular volume contraction—specifically a reduction in erythrocyte mass—which may be etiologic in the hyperadrenergic state.[188] Postural hypotension may be exacerbated by blunted postural responses of renin and aldosterone seen even in uncomplicated cases of diabetes.[189] Insulin itself may provoke postural hypotension in patients who have autonomic dysfunction, causing symptoms that may be confused with hypoglycemia.[190] Insulin may decrease or redistribute intravascular volume in excess of that explained by its hypoglycemic effect.[191,192] In recent studies insulin was shown to have direct vasomotor effects by increasing the blood flow of skeletal muscle, which illustrates the importance of sympathetic activation in maintaining the blood pressure following insulin injection.[193]

Less well appreciated than postural changes are changes in postprandial blood pressure in patients with autonomic dysfunction. Declines in systolic blood pressure of 25 to 75 mm of mercury have been recorded after a large meal and may be associated with symptoms of cerebral or cardiac hypoperfusion.[194] Similar changes have been found in patients with α-receptor blockade by phenoxybenzamine and postsurgical sympathectomy but the exact mechanisms have not been defined.[195] Amelioration of the hypotension may be achieved by consuming more frequent small meals or by the use of indomethacin.[195] Patients with presynaptic norepinephrine depletion have postsynaptic α-receptor proliferation and a supersensitive response to direct-acting sympathomimetics.[185,196,197] Hypertensive crises and intracerebral hemorrhage have occurred following the use of over-the-counter nasal decongestants containing sympathomimetic agents.[183]

A fall in the plasma glucose level normally elicits an asymptomatic parasympathetic discharge with bradycardia and mild hypotension, followed by sympathetic catecholamine release.[178] Hypoglycemia in a diabetic person who has autonomic dysfunction may result in a sudden loss of consciousness without premonitory signs.[198] A blunted epinephrine response to hypoglycemia may exacerbate underlying abnormalities in glucagon and growth-hormone secretion, resulting in a more rapid decline and prolonged depression of serum glucose in these patients.[199-203] Thus, altered glucose counterregulatory mechanisms and failure to ingest sugar due to the absence of symptoms place a neuropathic diabetic person at risk for severe hypoglycemia. Recent findings suggest that improved antecedent control of diabetes may enhance serum glucose recovery following insulin-induced hypoglycemia without altering blunted responses of counterregulatory hormones.[204]

Painless or unrecognized infarction in a person with diabetes may stem from autonomic neuropathy. Cardiac neuropathic changes have been described in diabetic patients dying from painless infarction.[56] As stated previously, although true painless infarction is uncommon, any person with diabetes who has an acute deterioration in clinical status should be evaluated for its presence.

Sudden cardiorespiratory arrests have occurred in patients with severe autonomic neuropathy.[205,206] Although cardiac arrhythmias commonly precipitate these arrests,[207] the role of the autonomic nervous system in regulating ventilation deserves mention. The parasympathetic nervous system is important to the integrity of normal ventilatory responses to both hypoxia and hypercapnia, in particular the increase in

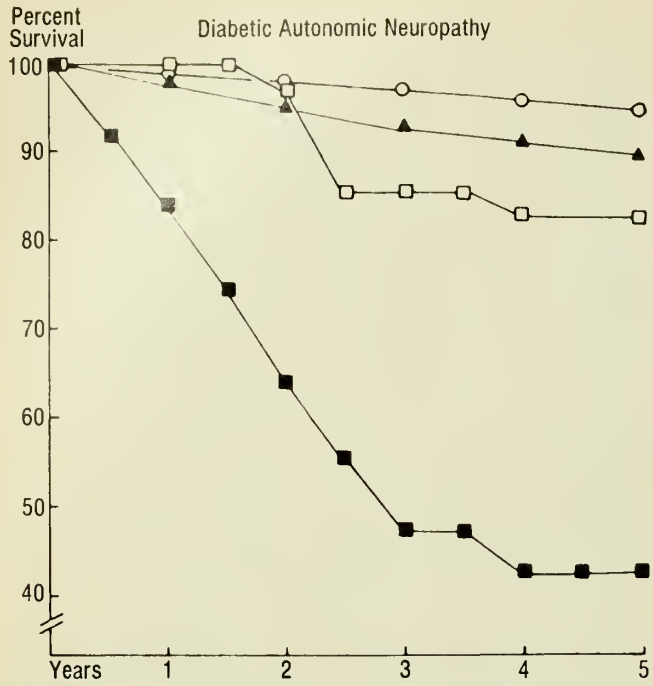

Figure 4.—Five-year survival curves for age- and sex-matched general population (o), age- and sex-matched diabetic population (▲), 33 symptomatic diabetic persons with normal (□) and 40 symptomatic diabetic persons with abnormal (■) findings on autonomic function tests.

respiratory frequency induced by these stimuli. In animals the ventilatory response to hypoxia or hypercapnia or both can be attenuated by vagal blockade or carotid body denervation.[208,209] The sympathetic nervous system is essential for increasing cardiac output and optimally distributing blood flow in response to hypoxia.[210] Hypoxia following α-adrenergic blockade has been associated with hypotension and bradycardia.[211] Although abnormal cardiovascular and ventilatory responses to hypoxia have been described in a few patients with autonomic dysfunction,[212] more recent studies have not shown abnormal responses in persons with neuropathic diabetes.[213]

Evaluation for abnormalities in autonomic reflex response can be done at the bedside in a simple, reproducible manner using readily available equipment. The most common abnormalities observed are parasympathetic dysfunction as reflected by loss of beat-to-beat heart rate variability in response to deep breathing, Valsalva's or standing.[172,180] Sympathetic reflex dysfunction can be detected by assessing blood pressure response to standing or to sustained isometric exercise.[179,180] It is better to assess response to a combination of maneuvers when evaluating a patient's condition. Patients are designated as having abnormal reflex function if the results of one test are clearly abnormal or if parasympathetic and sympathetic reflex tests both show borderline results. Abnormalities in reflex testing have been proposed to have prognostic significance. In one study, diabetic persons with autonomic dysfunction had a 56% five-year mortality compared with 11% for the general diabetic population (Figure 4).[169] Analysis of deaths in those with autonomic dysfunction showed a striking incidence (24%) of sudden death with no obvious cause at necropsy.[169] Assessment of the prognostic import of autonomic dysfunction alone is obscured by the more frequent occurrence of nephropathy, retinopathy and peripheral neuropathy in this population than in those with normal test results, and multivariate analysis has not been done.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Immunotherapy for Melanoma

QUESTION:

In the treatment of melanoma, is the following regimen of immunotherapy considered accepted medical practice: mixed respiratory virus (MRV), staphage lysate (SPL), bacille Calmette-Guérin (BCG) vaccine, methyl extracted residue of phenolized BCG (MER), and topical application of depigmenting agents?

OPINION:

In the opinion of the Scientific Advisory Panels on Dermatology, General Surgery and Internal Medicine, the following forms of immunotherapy in the treatment of melanoma are considered investigational: mixed respiratory virus (MRV), staphage lysate (SPL), bacille Calmette-Guérin (BCG) vaccine, methyl extracted residue of phenolized BCG (MER) and topical applications of depigmenting agents.

Medical Staff Conference

Problems in Diagnosing Pneumonia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *The topic for this conference is pneumonia and the difficulties encountered in identifying its cause. Michael Stulbarg will give the presentation.*

DR STULBARG:† Pneumonia, a microbial infection involving the airways and alveoli of the lung, is a problem that confronts physicians in every phase of medicine. Despite spectacular progress in the development of antibiotics, pneumonia remains the leading cause of death from infection and the fifth leading cause of death overall in this country. At least part of the failure in the treatment of pneumonia is due to the difficulty in promptly identifying the etiologic agent, and it is on this difficulty that I shall focus.

When confronted with a case of pneumonia, one may take an "empiric" approach to treatment, an approach that may be quicker and cheaper but that is intellectually less satisfying than a "specific" approach. With the empiric approach, one begins immediate treatment based mostly on epidemiologic factors such as the circumstances of acquiring pneumonia—that is, community- versus hospital-acquired infections—or the presence of underlying disease. The specific approach, in which one attempts to identify the etiologic agent, is much slower and may involve a cascade of procedures. This approach sometimes uncovers unexpected causes and may lead to more effective therapy, but it may also result in delaying initiation of therapy for common causes of infection.

The difficulty in the empiric approach to treating pneumonia is emphasized by some recent data from a review of 1,000 patients with pneumonia seen at Yale from 1969 to 1972, compared with a similar group seen between 1979 and 1982.[1] The study shows that the incidence of bacterial pneumonia fell from 64% to about 50%, but—perhaps more dramatic—the incidence of pneumococcal pneumonia fell by more than 50%, from 46% to 21% of all causes. Tuberculosis remained constant at 4%, but fungal pneumonia nearly doubled in frequency from 7.2% to 13.2%. Viral pneumonia also nearly doubled in frequency from 17.5% to 32.9%. *Pneumocystis* and *Chlamydia* each accounted for about 2% of cases of pneumonia in 1979 to 1982; neither even appeared in the 1969 to 1972 group. Although these changes may in part reflect changes in patterns of referral or in the use of new diagnostic tests, the large number of possible etiologic organisms makes empiric therapy more difficult than it has ever been before.

Besides the widening spectrum of organisms, other problems in the diagnosis of pneumonia include new patient populations, such as immigrants and immunosuppressed patients with their unusual infections—especially patients with the acquired immune deficiency syndrome (AIDS) who are presenting with opportunistic infections previously seen only in profoundly immunodeficient persons. Furthermore, the development of many new diagnostic procedures may bewilder internists trying to choose which procedures to request or permit for their patients.

I will discuss these procedures with their respective yields and complication rates and the limitations of each. I will begin by presenting one of our recent cases that epitomizes many of the problems faced in diagnosing pneumonia and shows the dilemma of choosing between empiric and specific treatments guided by invasive diagnostic studies.

Report of a Case

The patient, a 40-year-old gay man, presented with a right midlung infiltrate, fever, cough and blood-streaked sputum. He had previously been in good health, though he was a smoker. He was seen at an outside emergency room because of malaise for a week

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and chills for four days. A diagnosis of pneumonia was made and a regimen of penicillin by mouth was begun. Four days later, because of exacerbation of his symptoms of cough, fever and chills and the new development of blood-tinged sputum, he came to the Moffitt Hospital (University of California, San Francisco) emergency room and was admitted with a large right mid-lung field consolidation (Figure 1). Sputum Gram's stain showed many leukocytes but no predominant organism, and culture grew only mixed oronasal. flora. Treatment with tobramycin and cefamandole was begun because the patient had been treated previously with penicillin and had not improved. On the day after admission cavitation appeared in the lung infiltrate (Figure 2) and the pulmonary service was consulted regarding whether or not the broad-spectrum antibiotic coverage was adequate and whether or not a diagnostic procedure should be done. On our recommendation, a needle aspiration was done under fluoroscopic guidance. The return was scanty and Gram's stain of the specimen was negative, so a regimen of tobramycin and cefamandole was continued. Three days later, blood cultures were still negative, but the needle aspirate grew out *Streptococcus pneumoniae,* a particularly surprising finding because he had been taking penicillin for four days and tobramycin and cefamandole for one day when this aspiration was done. With this specific diagnosis, we changed the therapy to penicillin, a simpler, safer and cheaper antibiotic, and the patient recovered.

Figure 1.—Chest roentgenogram showing right midlung consolidation.

Figure 2.—Chest roentgenogram 24 hours later showing cavitation of the pneumonic process.

This case illustrates the central question: Was it appropriate to do the needle aspiration or would it have been better just to treat him with tobramycin and cefamandole for seven to ten days and to accept the intellectual dissatisfaction of never having a specific diagnosis? The question of the need for an invasive procedure is common, for history and physical examination are notoriously unhelpful for making a specific etiologic diagnosis in patients with pneumonia. The presence of pneumonia is commonly suggested by the symptoms of fever, cough and sputum and physical findings of rales and dullness, but rarely does a history suggest a cause. Specific clues—such as exposure to dying birds—are helpful, but they are unfortunately rare. The findings from a chest radiograph are similarly nonspecific. In general, a diffuse pattern fits more with viral, fungal or tuberculous infection, and a localized pattern is more suggestive of a bacterial process, but no pattern is pathognomonic of any specific infection. Thus, like the history and physical examination, the radiographic findings point to the need for a diagnosis, but not to a specific organism.

Regarding laboratory tests, blood cultures may be of help, but they are positive in cases of bacterial pneumonia only about 10% to 20% of the time. Serologic studies, when available, take weeks to months to provide results and certainly do not help immediately. A test for circulating antigen is currently available only for *Cryptococcus*. It is helpful when positive, but cryptococcal pneumonia is rare and false-negative results may occur. Cold agglutinins, which are included in almost every physician's list of tests to be ordered in a workup for pneumonia, are low both in sensitivity—being positive in only about half of patients with *Mycoplasma*—and in specificity—being positive in patients with various other types of pneumonia, particularly influenza and adenovirus infection. Skin testing is helpful epidemiologically and in identifying cases of possible reactivation of tuberculosis, but are rarely of help in the immediate workup of a patient with pneumonia.

Finally, we come to sputum, which has been the focus of most attention in diagnosing pneumonia.[2] The classical teaching is that one should look at a Gram's stain of a carefully selected portion teased out from

sputum produced by a deep cough, and if one finds numerous epithelial cells, the specimen is considered unrepresentative and contaminated by oral flora. On the other hand, the finding of clumps of neutrophils with a predominant organism is thought to reflect the cause of the pneumonia, permitting presumptive treatment. Unfortunately, such clear-cut Gram's stains are rarely found. This approach to pneumonia is summarized in an algorithm (Figure 3). If the Gram's stain is positive for a predominant organism, treatment is begun and the patient's condition is reevaluated in 48 hours. If the patient is better, treatment is continued. If the patient's condition is not improved, we then consider either broadening antibiotic coverage or proceeding with a diagnostic procedure—transtracheal aspiration, needle aspiration, bronchoscopy or open-lung biopsy. Even if the sputum Gram's stain is negative, one may choose to begin empiric treatment and go through the same process of reevaluation in 48 hours. Alternatively, one can go directly from an unrevealing Gram's stain to a diagnostic procedure. This choice is not an easy one, and while it is made somewhat easier by knowing the yield and limitations of invasive diagnostic procedures, there is no simple solution.

Because sputum has been the focus of most attention in the diagnosis of pneumonia, the problems in its evaluation are of particular note. First of all, there is considerable difficulty simply in getting patients to expectorate. Patients are often not instructed what to do, namely, to rinse their mouth and cough deeply, clearing sputum from the respiratory tract rather than from the mouth. Contamination is inevitable because sputum must pass through the mouth, where the concentration of bacteria varies from 1 million on the dental surfaces to 1 billion in saliva.[3] Even with repeated washings of sputum specimens, one cannot prevent contamination with oropharyngeal flora. After sputum is produced, frequently delays at the bedside or at the nursing station further reduce the value of the specimen. In the laboratory, major problems bedevil interpretation of a Gram's stain.[3] Even the choice of which area of sputum to examine may dramatically affect the interpretation. A Gram's stain is also used to decide if a sputum specimen is even worth culturing. In our laboratory, sputum is considered adequate for culture if there are fewer than ten epithelial cells per low power field. However, in a recent report, 391 sputum specimens were examined and their acceptability for culture evaluated by comparing six different methods described in the literature.[4] As agreement was reached by all six methods in only 60% of the specimens, the decision to culture an individual specimen would vary considerably among different laboratories. Contamination with oral flora is a major problem no matter what care is taken in collecting the specimen and overgrowth of pathogens by normal flora is frequently found. Sputum is useless for interpretation of anaerobes because of their invariable presence in the mouth. Even if an acceptable sputum specimen reaches the laboratory, the delay in obtaining culture results makes it even more difficult to make an initial decision on therapy (Table 1). Despite these problems, we have to make rapid decisions about treatment, especially when a patient is very sick or deteriorating.

TABLE 1.—*Time Delay for Culture Results*

Organisms	*Growth Time*
Aerobes	24-48 hours
Anaerobes	48-72 hours
Legionella	5-15 days
Viruses	2-28 days
Fungi	2-21 days
Mycobacteria	2-8 weeks

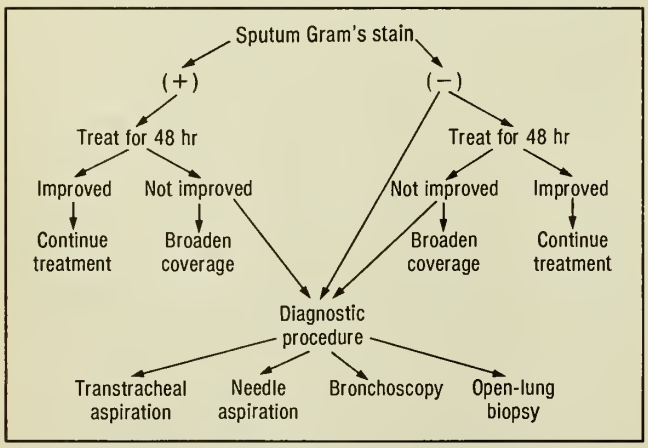

Figure 3.—Algorithm: Approach to pneumonia. (+) Indicates the presence and (−) the absence of a predominant organism on Gram's stain of the sputum specimen.

The failure of the sputum to elicit a diagnosis leads to consideration of the available pulmonary diagnostic techniques: (1) sputum induction such as by inhalation of hypertonic saline, which is listed here to emphasize its usefulness and simplicity; (2) transtracheal aspiration; (3) fiberoptic bronchoscopy, especially bronchoalveolar lavage and transbronchial biopsy; (4) needle aspiration biopsy—we use only aspiration, for the cutting technique has been abandoned because of high complication rates, and, finally, (5) open-lung biopsy, the "gold standard."

Pulmonary Diagnostic Procedures

Transtracheal Aspiration

Transtracheal puncture was originally developed for doing transcricoid bronchography, but was adapted in the 1950s for aspirating specimens from the lower respiratory tract uncontaminated by oropharyngeal flora.[5-7] With this simple technique, an intravenous type catheter (14- or 16-gauge) is introduced through the cricothyroid membrane into the distal trachea. Suction is applied either with a syringe or with wall suction via a sputum trap and the specimen obtained is *immediately* cultured for both aerobes and anaerobes. If no secretions are obtained, one instills and immediately aspirates a small amount of nonbacteriostatic saline. Although Gram's stain of this material is said to be helpful, my

experience is that Gram's stain is rarely helpful, but that the culture results often are.

The literature does not provide a consensus about the usefulness of this technique. The largest and best series is that reported in 1977 by Bartlett.[7] He looked at nearly 500 cases of pneumonia in patients who were thought probably to have bacterial infections. He decided primarily on clinical criteria (only 23 of the patients had positive blood cultures) that 351 out of the total of 369 positive aspirates were "true-positives" for etiologic pathogenic organisms. In all, 18, or 4%, were considered false-positive as other diagnoses were found to explain the pulmonary infiltrates; 24% of the cultures of the aspirate specimens were negative, but nearly half of these were attributable to prior antibiotic therapy. Bartlett concluded that this is a highly reliable technique as long as a patient is *not* already on antibiotic therapy. Surprisingly, good results such as these have not resulted in the continued use of this procedure either in our institution or in many others. This may be because the procedure is anxiety-provoking for both physician and patient, but a recent report of 1,210 transtracheal aspirations found the complication rate to be low, in that in 6 out of 1,210, or 0.5%, moderate to severe subcutaneous emphysema developed, 0.2% had significant hemorrhage and in 0.2% paratracheal infections developed.[8] There were no deaths reported in these 1,210 cases, though several deaths have been reported elsewhere.[9,10]

I had to go back to 1977 to find a case at the University of California, San Francisco, in which transtracheal aspiration was helpful. A 63-year-old woman presented with a waxing and waning left lower lobe infiltrate. She was finally admitted to hospital and a transtracheal aspirate showed a pure culture of anaerobic flora. She was treated with chloramphenicol with total resolution of the infiltrate.

Fiberoptic Bronchoscopy

Fiberoptic bronchoscopy is the procedure that has put pulmonology on the medical map. Unfortunately, this procedure has not been of much use in diagnosing bacterial pneumonia, probably because the bronchoscope invariably passes through a highly contaminated area, the oronasopharynx, before entering the lungs. In one study, 45 patients underwent transtracheal aspiration followed by fiberoptic bronchoscopy.[11] In 31 of the 45 transtracheal aspirates, all cultures were negative, whereas only 6 of the fiberoptic bronchoscopy specimens were culture negative. Only 14 of the transtracheal aspirates showed potentially pathogenic bacteria (a total of 21 different strains), in contrast to the 39 bronchoscopy specimens that were positive for potential pathogens (a total of 73 different strains). The authors assumed that the transtracheal results were more accurate, and that most of the organisms found on bronchoscopy represented contaminants. In response to this failure of bronchoscopy, Bartlett and colleagues developed a very clever brush within a double catheter and a distal absorbable plug that could be displaced in the lower airway before the brush was advanced.[12] Their initial results suggested that with this technique one could pass through contaminated secretions and still get reliable distal specimens. In their more recent paper they report on 65 patients, including 10 patients who had bacteremic pneumonia.[13] In all ten cases the catheter was able to isolate the etiologic organism in concentrations of 10,000 or more. In several cases they did obtain additional pathogens, but in every case the concentration was too low to be considered important. By contrast, Fletcher and coworkers recently reported the results of bronchial brushing in 13 patients with pneumonia proved to be bacterial by transthoracic needle aspiration, autopsy or blood culture. They compared the new double-lumen protected brush with the traditional unplugged single-lumen brush and found no advantage to the newer brush. Using both types of brushes, one of the etiologic organisms was identified in 10 of 13 cases (77%). With both procedures one of the etiologic agents was missed about two thirds of the time, and in a similar number both brushes isolated nonetiologic organisms. Their conclusion was that the protected brush offered no advantage over the standard unplugged brush and that both frequently yielded false-positive and false-negative results. Our own limited experience with the plugged double-catheter brush has not been very encouraging and, at least so far, its initial promise does not seem to be holding up.

Transbronchial biopsy has become a regular part of the fiberoptic bronchoscopy procedure only in the past several years.[15-19] This procedure has been tremendously helpful in the diagnosis of diffuse infiltrates and localized masses or lung infiltrates. A biopsy forceps is passed under fluoroscopic guidance into an area of abnormality, the forceps opened and multiple bites taken. Our results and those reported by others have been encouraging, particularly in immunocompromised patients. Although a large percentage (30% to 50%) of cases show only nonspecific changes, which are not enough to rule out the presence of significant disease,[17-19] the overall rate of specific diagnosis is 41%, rising to 52% with the addition of bronchial brushing.[8] This diagnostic rate justifies frequent use of this procedure in these patients. The interpretation of negative or nonspecific results is still controversial.[17,18]

In deciding about the usefulness of a procedure, we must also look at its safety record. Transbronchial biopsy has done well.[20] The incidence of pneumothorax is 5% to 7%[20] and significant hemorrhage is reported to occur in 1%; I suspect it does not occur even that often. There is approximately one death per 500 patients, but many of those undergoing the procedure are very sick. So this is a reasonably safe procedure, and I believe that bronchoscopy with transbronchial biopsy is a reasonable early step in an immunosuppressed patient with an undiagnosed infiltrate.

An example of such a patient is a 53-year-old woman whom we saw two years ago. She presented with patchy bilateral lower lobe infiltrates (Figure 4),

cough, shortness of breath, some minimal low-grade fever and malaise. Transbronchial biopsy showed noncaseating granulomata, but special stains showed rare acid-fast organisms. These infiltrates cleared completely with only antituberculous therapy.

What about bronchoalveolar lavage? This is a relatively new procedure that was originally described for use in the staging of immunologically mediated interstitial lung disease. Most of us have found it disappointing for that use, but so far it looks very encouraging for diagnosing infectious pneumonia.[21,22] To do bronchoalveolar lavage, the bronchoscope is wedged into the periphery of the lung and multiple 20-ml aliquots of normal saline solution are instilled and aspirated. A total lavage of 80 to 120 ml usually yields a specimen of 30 to 60 ml. A large area of lung can be sampled with this technique. This procedure is remarkably well tolerated by most patients, even those who cannot undergo biopsy because of mechanical ventilation or a bleeding diathesis. We have seen several patients in whom bronchoalveolar lavage was diagnostic despite a transbronchial biopsy specimen that showed no abnormalities. This has been particularly true in patients with AIDS complicated by *Pneumocystis* pneumonia.[23] It may be that a Gram's stain of the lavage specimens will be useful in cases of bacterial pneumonia despite contamination of the cultures by oronasal flora.

TABLE 2.—*Needle Aspiration of Pulmonary Infiltrates*

			Range Percent
Results*			
No. infections found / No. procedures	= 151/255	59%	12%-100%
No. infections found / No. total infections	= 151/218	69%	50%-100%
No. infections missed / No. negative procedures	= 67/104	64%	13%- 83%
Complications*			
No. serious complications / No. procedures	= 35/238	15%	0%- 31%
No. deaths	2/238	1%	

*Six studies 1972 through 1981.

Needle Aspiration

Needle aspiration is probably the most powerful of the techniques used for nonthoracotomy diagnosis of bacterial pneumonia. First reported nearly 100 years ago, it gained considerable popularity in the early part of this century when it was important to identify specific serotypes of *Pneumococcus* to guide specific serotherapy. The procedure has also been popular among pediatricians. With this simple technique, a spinal or a modified needle is passed percutaneously into the area of abnormality, suction is applied and if nothing is returned a small amount of nonbacteriostatic saline is instilled and then aspirated. In six studies reported from 1972 to 1981 (Table 2),[24-29] the overall yield was 59% for infection, considerably higher than for bronchoscopy, though the population studied was quite different. If one looks only at the 218 who subsequently proved to have infection, the yield was 69%. If the results were negative, however, infection was often missed. Of the total of 104 procedures reported negative, 67 represent missed infections. That indicates a 64% false-negative rate, so a negative result from needle aspiration by no means rules out infectious pneumonia. The complication rate for needle aspiration is considerably higher than that for bronchoscopy. The 16% incidence of serious complications includes pneumothorax requiring a chest tube, significant hemorrhage, air embolism and a mortality of about 1%.

Two cases may be used as examples: The first is

Figure 4.—Chest roentgenogram showing bilateral diffuse lower lobe infiltrates.

Figure 5.—Chest roentgenogram showing right upper lobe cavity.

that of a 29-year-old man with leukemia whom we were asked to see because of an expanding right upper lobe infiltrate with cavitation (Figure 5). The sputum, transtracheal aspiration and fiberoptic bronchoscopic specimens all grew *Bacillus cereus*. This is a very uncommon pathogen and we were reluctant to believe the results until we actually obtained the organism from within the cavity. This patient did respond to appropriate gentamicin therapy in high doses. The second case is that of a 73-year-old man who presented with fever, cough, hemoptysis and a large right upper lobe infiltrate. Results of sputum examinations and fiberoptic bronchoscopy were negative, though bronchoscopy induced a high spiking fever requiring a week of antibiotic therapy in hospital. The patient refused further diagnostic procedures and went home, but returned three weeks later with considerable enlargement of his right upper lobe infiltrate (Figure 6). This time we did a needle aspiration, which elicited the diagnosis of adenocarcinoma, but unfortunately a large pneumothorax developed that did not respond to chest tube placement and the patient ultimately required thoracotomy. Thus, needle aspiration is a powerful technique, perhaps underused, but not without serious complications.

Open-Lung Biopsy

Open-lung biopsy, long considered the gold standard, has been widely used for identifying the cause of diffuse lung infiltrates[19] and has been applied in more recent years to identify the cause of infections in immunosuppressed patients.[8,30,31] A biopsy of the right middle lobe can be done through a small anterior thoracotomy. This has even been done under local anesthesia. However, if one wants to choose the biopsy site under direct vision, or to obtain multiple specimens, then a larger thoracotomy, with all of its attendant risks, may be required. Not surprisingly, the yield from open-lung biopsy is higher than from all other procedures—69% in a recent collected series of 288 patients.[8] Nonspecific reactions were found in a high percentage, nearly 30%.[8] The difference is that with open-lung biopsy one is willing to accept a nonspecific reaction as being truly representative of the underlying pathology. But open-lung biopsy is by no means perfect. In one report 4 of 20 cases of tumor or infection were missed, and in two of these four the diagnosis was made by transbronchial biopsy.[30] In four other cases, the tissue was inadequate for diagnosis.[30] The complication rate, as would be expected, is much higher than for the other procedures, though perhaps not as high as we often fear. In the series of 288 thoracotomies in immunosuppressed patients (see above), the overall complication rate was 11%. Most of these complications were pneumothoraces, not usually considered a major complication after open-lung biopsy.[8] Other less common complications—hemothorax, wound hematoma, hemoptysis, wound dehiscence, chest pain after the operation and tumor recurrence at the chest tube site—are all important. The death rate is low; it is reported here as 0.6%.[8]

A potentially more important question is whether we accomplish anything with open-lung biopsy. A group at Stanford Medical Center has addressed this point very carefully in 83 immunosuppressed patients undergoing open-lung biopsy.[31] They found that whether or not the open-lung biopsy resulted in a specific diagnosis or in change of therapy, there was no difference in outcome. Of the 37 whose treatment was altered, 20 (54%) survived, as opposed to the 46 whose treatment was not altered, of whom 18 (39%) survived. Though this appears to favor an aggressive

Figure 6.—Chest roentgenograms showing progression of a right upper lobe infiltrate over a two-week interval.

diagnostic approach, the difference did not reach statistical significance. These authors wondered whether we are really accomplishing anything with open-lung biopsy in this type of patient.

Conclusions

Coming back to our patient with an undiagnosed infiltrate who has symptoms suggestive of pneumonia, one must decide whether to treat empirically based on the background of the patient or whether to do a diagnostic procedure. Despite all the data on diagnostic procedures that have been summarized here, the indications for invasive procedures to define the bacteriology of the lower respiratory tract are still not well defined. Having a specific etiologic diagnosis makes treatment easier and safer and also considerably cheaper by avoiding some of the newer, very expensive antibiotics. Unfortunately, there is no simple algorithm that will routinely lead to a specific diagnosis. One must make decisions on an individual case basis, weighing the dangers of whatever broad-spectrum therapy is contemplated against the dangers of the specific procedure(s). Even when the decision is to do a procedure to make a specific diagnosis, the smears may be negative and there may still be a wait of days to weeks for positive culture results, so the necessity for empiric therapy is not obviated by doing any of these diagnostic procedures. If any invasive procedure is to be used, the choice depends not only on reported yields but also on local expertise and a patient's ability to withstand a cascade of procedures. In other words, the sicker a patient, the more a physician may want to go directly to the procedure of highest yield—open-lung biopsy. Finally, the sicker and more complex a patient, the more important it is to treat broadly while awaiting results of whatever tests or procedures are done.

QUESTIONS AND ANSWERS

PHYSICIAN IN THE AUDIENCE: *Is there any role for nasotracheal aspiration?*

DR STULBARG: Nasotracheal suctioning may help get a good sputum specimen. Contamination occurs because the catheter passes through the nasopharynx, but it is a reasonable part of the effort to get a good specimen in a patient who cannot cooperate.

PHYSICIAN IN THE AUDIENCE: *What can be done to overcome the lack of use of transtracheal aspiration?*

DR STULBARG: Your question implies that something should be done. I have had much experience with this procedure and have never had a serious complication, but it is anxiety-provoking every time. It is difficult but important to balance in each case the need for information with the danger of the procedure(s) being considered. If the procedure were done in a wholesale way, as it was 10 to 15 years ago, it might be quite dangerous. If it were treated as a special procedure requiring special instruction it could be a useful adjunct. I would like John Conte to comment on that particular point.

DR JOHN CONTE:* I have no better answer. The data are quite clear that transtracheal aspiration is a high-yield procedure. It has never been clear to me either why we do not use it more. We recommend it frequently. I suspect that this has to do partly with the ever-broadening potency of antibiotics that are used empirically.

DR BOUSHEY:† It could be a local tradition. I recall that in 1969 when the procedure was first being advocated, it caused death in one of the patients here. This may have discouraged the development of a local tradition of use.

DR STULBARG: There are several deaths reported, and one has to realize that it is a dangerous procedure.[12,13] When I first learned the technique it was being done on most patients who had pneumonia, which is inappropriate. It should be considered in the diagnostic armamentarium, but I would prefer to have it restricted to those who have special training.

DR SMITH: *We are very happy to welcome back Dr Don Ganem, who spent this past year at the Brigham and Women's Hospital in Boston. Don, were you using transtracheal aspiration there?*

DR GANEM:‡ We did not use it for the same reason; that is, there was no local expertise. It was, however, done widely by house staff at the Massachusetts General Hospital. Our thoughts are that the procedure is most reasonable in patients such as renal transplant recipients, who have adequate leukocytes but who are at risk for unusual infections because of immunosuppression. Previously healthy patients admitted with pneumonia can usually be treated adequately without invasive procedures.

PHYSICIAN IN THE AUDIENCE: *I am interested in your comments that in your experience open-lung biopsy rarely adds to the information gained from transbronchial biopsy. Do others have a similar experience?*

DR STULBARG: We need to distinguish patient populations. In patients with indolent noninfectious processes, open-lung biopsy gives a much higher yield than transbronchial biopsy because it permits definition of the pattern of the disease.[19] In immunosuppressed patients with pulmonary infiltrates the experience is more variable. Dr Katzenstein, a pathologist, reported an extensive experience at Washington University but that open-lung biopsy added very little to transbronchial

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biopsy.[17] The experience of others is that open-lung biopsy adds a great deal.[18,30,31]

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Epitomes

Important Advances in Clinical Medicine

Physical Medicine and Rehabilitation

The Scientific Board of the California Medical Association presents the following inventory of items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in physical medicine and rehabilitation that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 44 Gough Street, San Francisco, CA 94103

Mechanical Prophylaxis of Deep Vein Thrombosis

SHORT-TERM AND LONG-TERM complications in dealing with deep vein thrombosis have been known for many years and range from mild swelling in the lower extremities to sudden death. It is obvious that the best treatment is prophylaxis and multiple means have been used over the years including, but not limited to, range-of-motion exercises, low doses of heparin and mechanical compression.

Mechanical means of prophylaxis of deep vein thrombosis in the form of elastic stockings have been in use for many years with varying degrees of success. Their mechanism of action is by circumferential compression of soft tissues, with the greatest amount of pressure being distal and progressively decreasing as the stockings go higher up the leg.

Unfortunately, the diameters and configuration of patients' lower extremities vary greatly, which leads to some compromise in the fit of the devices. After a number of washings, the elastic garments also tend to stretch and lose their uniform compressive effect.

The advent of custom-made elastic garments overcomes these problems to a large extent, but the high cost and difficulty in application make them impractical for many persons.

In the mid 1970s, the intermittent compression pump was introduced as a means of prophylaxis for deep vein thrombosis. The mechanism of action is by intermittently inflating a balloonlike garment over the lower extremities. By doing this, one can introduce intermittent compression of the calf veins of the leg. The mechanics of the device are said to simulate the muscle pump mechanism, which is lost or reduced in those persons who are paralyzed or confined to bed.

In 1980 Rossi and associates did a prospective controlled study in 18 patients with spinal cord injuries to establish the incidence of deep vein thrombosis using daily examination, impedance, plethysmography, fibrinogen scans and venograms. The incidence of deep vein thrombosis in untreated patients was 78%.

In 1982 the study was repeated using intermittent compression of the lower extremities as a means of prophylaxis, with a decrease in the incidence of deep vein thrombosis from 78% to 33%.

In those patients using external pneumatic compression in whom deep vein thrombosis did develop, all clots were in the popliteal or calf veins as opposed to 23% being in the iliofemoral veins in the untreated group.

There were no noticeable complications from the use of external pneumatic compression. The devices are easy to use, simple to apply and can be left in place 24 hours a day except for skin checks and bathing. The only significant precaution is that they must be applied low enough toward the ankle to prevent venous pooling.

The routine use of intermittent pneumatic compression of the lower extremities of bedridden patients is a very promising addition to the current methods of preventing deep vein thrombosis and in some institutions

has already become a routine method of prophylaxis in postoperative and bedridden patients.

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Delayed Effects of Poliomyelitis

MOST PHYSICIANS have thought of poliomyelitis as a relatively static disease that stabilizes after the initial febrile stage of paralysis. That opinion was shared by their patients, who found that after months or years of diligent exercise they had increased strength so that they were able to discard braces or walk after being confined to wheelchairs. Now, 30 and 40 years after the polio epidemics, increasing numbers of polio survivors are finding themselves unable to perform self-care tasks or to do the work that they had been doing for years. To polio survivors who believed their condition to be stable, these unexpected limitations are confusing and distressing.

In the past 18 months we have seen 35 polio survivors whose common symptoms were fatigue, pain, decreasing strength or loss of function. Ages ranged between 30 and 84 years. A decreased ability to perform self-care tasks or to ambulate was frequently associated with pain due to degenerative arthritis secondary to muscle imbalance. The joints commonly involved were shoulder (15), knee (8), hip (5), ankle/foot (4) and wrist (2). Other causes of pain and disability included carpal tunnel syndrome (6), tension headache (5), fibrositis syndrome (3), bursitis/tendinitis (3) and thoracic outlet syndrome (1). All of the patients had scoliosis and many had back pain because of degenerative disc disease (15), spondylosis (8), sacroiliac joint pain (7) and lumbar spinal cord stenosis (3). Though unaccompanied by pain, increasing joint laxity and muscular contracture accounted for increasing disability in 23 patients. Fatigue was a frequent complaint (26) unexplained by anemia, electrolyte disturbance or hormonal dysfunction.

Perhaps most frightening to some polio survivors is the gradual or sometimes sudden onset of progressive weakness (20). In some cases the weakness was explained by radiculopathy (4), lumbar stenosis (3), compression neuropathy (7) or brachial plexitis (1). In these cases the weakness was accompanied by pain, numbness or other appropriate symptoms and signs. In others (5) the weakness was not associated with pain or any other symptoms except fasciculation or a sense of impeding cramp. The weakness was limited to muscle groups previously weakened by poliomyelitis. Alter and other authors have described late progression of weakness in postpolio patients though the cause or mechanism is unknown. Wiechers and Hubbell have studied postpolio patients with single-fiber electromyography, with findings consistent with defective neuromuscular transmission in reinnervated motor units.

Progressive resistive or strengthening exercises have not been helpful in cases of late progressive weakness. In fact, patients have been cautioned to avoid excessive or exhausting exercise. Swimming remains the best form of exercise for the conditioning effect while unloading painful or arthritic joints. Regardless of the cause of decreasing function, patients are encouraged to practice joint and energy conservation in their activities of daily living and in their work situations.

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Sexuality and Disability

IN THE PAST, physically disabled persons were often seen as asexual—without sexual needs, desires or capabilities. Professionals avoided dealing with sexual dysfunction due to lack of training, personal discomfort and a feeling of futility about therapeutic attempts.

This negative stereotype is difficult to sustain in view of the growing literature and research on the subject. For example, we know from the studies of Bors and Comarr that 96% of men who are quadriplegic from cervical spinal cord injury are capable of having an erection and that more than 72% of these men can have intercourse. A recent study of stroke survivors indicates that 73% of the women and 88% of the men retain sexual desire following their disability, and 46% of the men retain the ability to achieve erection.

Today when a person suffers paralysis, amputation, arthritis, cardiopulmonary disease or other illness, modern sex education, counseling and therapy techniques are integrated into the rehabilitation plan to develop sexual capacities to the fullest possible extent.

The goal of sex education is to impart accurate information to all patients who wish to know about sexuality and the effects of disability. Classes, books and movies can be effective supplements to teaching positioning (arthritis, back pain, stroke), the management of incontinence (paraplegia, quadriplegia, ostomy), energy cost of intercourse (cardiopulmonary disease) and side effects of drugs (hypertension, multiple sclerosis).

Sexual counseling is additionally used for those with specific sexual conflicts or needs. Counseling may help with body image concerns (mastectomy, amputation, burns), to decrease performance anxiety, to dispel myths, to broaden attitudes regarding sexual options and to improve ability to communicate effectively about sexual issues. Social skills training is especially helpful for the congenitally disabled.

Sex therapy is needed by the relatively few disabled persons whose problems are not resolved by education and counseling. An intensive individualized program includes sensate-focus exercises most commonly for the treatment of erectile dysfunction, premature ejaculation or anorgasmia. It can also be used as a therapeutic trial

before the insertion of a penile prosthesis (diabetes, nephropathy).

With the advent of these approaches, it has become clear that physical disability does not necessarily lead to sexual disability.

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Urinary Infection in a Neurogenic Bladder

NEUROGENIC BLADDER DYSFUNCTION can occur due to traumatic and other lesions of the spinal cord such as multiple sclerosis, tumors, diabetes mellitus, stroke and the like. The resulting bladder dysfunction causes disturbances in normal micturition. In many patients with such dysfunction, use of an indwelling catheter may be eliminated by intermittent catheterization, therapy with α-sympathetic blockers or transurethral surgical repair (or all three). Bacterial colonization or obvious urinary tract infection continues to be a common occurrence, particularly in patients who wear external collecting devices and a leg bag. Urinary tract infections are a major cause of mortality in patients with spinal cord injury and neurogenic bladders.

Diagnosing urinary tract infections by symptoms alone in patients with neurogenic bladders is unreliable. Lack of symptoms such as fever, chills, dysuria and flank pain, in spite of significant bacteriuria (greater than 100,000 per ml), continues to be common in most patients with spinal cord injury who have unobstructed voiding. In an unpublished study by Perkash and coworkers (1982), only 3% of 103 patients with spinal cord injury had symptoms, in spite of bacteria in a urine specimen numbering more than 100,000 per ml. Thus, symptoms per se are poorly correlated with significant bacteriuria in such patients. Due to this lack of clinical signs, bacteriuria poses a therapeutic dilemma in treatment and management. In addition, with complicating factors of perineal and drainage bag contamination, the question of colonization versus true tissue invasion arises. Quantitating urine pyuria has proved helpful for clinically determining urinary tract infection. Microscopic examination of urine sediment for the presence of leukocytes is a time-honored technique, but one that is poorly standardized and thus semiquantitative. Quantitating pyuria, however, is a simple and logical improvement of this technique. The usefulness of hemacytometer counting of uncentrifuged urine leukocytes in urine specimens of a general hospital's inpatients was reported in 1976. The presence of 10,000 or more leukocytes per ml of urine was correlated with the presence of a urinary tract infection. In another (unpublished) study, the presence of more than 10,000 leukocytes per ml of urine was highly predictive of the presence of bacteriuria in men with spinal cord injury.

As a result of our continued investigations to define and manage urinary tract infection in a neurogenic bladder, certain general guidelines have been developed. For patients being maintained on indwelling Foley catheter drainage, only symptomatic bacteriuria associated with fever and chills is treated; otherwise, no antimicrobial treatment or prophylaxis is recommended. Patients catheterized intermittently who remain asymptomatic despite significant bacteriuria are not generally treated. Due to regular, timed bladder emptying, bladder bacteriuria, if due to simple colonization, could be transient and thus flushed out at the next catheterization. However, if a patient has bacteriuria and symptoms of fever and chills, treatment is based on the urine culture-sensitivity report. Finally, patients receiving external condom drainage who have asymptomatic bacteriuria with fewer than 10,000 leukocytes per ml of urine may not require treatment if the bladder is draining adequately. This type of bacteriuria could be a contaminant from a patient's own perineum or drainage bag. Attention towards maintaining proper hygiene might be the only recourse for reducing or controlling the incidence of asymptomatic bacteriuria.

The recent development and use of noninvasive "markers" to define a site of infection and therefore direct the most effective type of treatment is now being studied. Surface blockers or specific antipilial antibodies available to prevent bacterial adhesion and colonization on the bladder mucosa may provide a lasting cure.

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Electrodiagnosis in Brachial Plexus Injury

FOLLOWING brachial plexus injury, electrodiagnostic changes are seen most commonly during needle electromyography. Changes in nerve conduction velocity studies are much less common because, one, plexus injuries most often produce axonal loss rather than demyelination and, two, there are many technical problems with brachial plexus nerve conduction studies.

The electromyographic examination must include the infraspinatus and supraspinatus, rhomboid, levator scapulae, serratus anterior and cervical paraspinal muscles to accurately assess the proximal extent of plexus injury.

Although changes in motor or sensory conduction velocities are not common in plexopathy, a reduction in amplitude of the motor or sensory evoked potential is common. Abnormalities of conduction or evoked-potential amplitude change may be most common in the musculocutaneous nerve. The role of F-wave stud-

ies is controversial, while the value of studies such as C-8 root stimulation remains to be determined.

An important issue in traumatic plexopathy—and one of the major uses of sensory conduction testing—is the attempt to differentiate between preganglionic and postganglionic lesions. With complete sensory loss in a given dermatome, a normal sensory nerve action potential suggests a preganglionic lesion (root avulsion) whereas an absent response suggests a postganglionic lesion if the study is done at least five days after the injury.

Recently the value of somatosensory evoked potentials in the electrodiagnosis of traumatic brachial plexopathy has been established. They seem to be particularly useful in differentiating preganglionic and postganglionic lesions. Three components of the somatosensory evoked potentials are used: N9, N13 and N20. N9 is thought to arise from the brachial plexus and its amplitude is diminished only by a postganglionic lesion. N13 arises in the cervical cord or brain stem, while N20 is a cortical potential. N20 and N13 amplitudes would be affected by either a preganglionic or a postganglionic lesion. Amplitude attenuation of greater than 40% compared with the opposite side is the critical value. A comparison of N9 and N13 amplitudes is used to delineate the degree of preganglionic involvement. If the N9 amplitude decrease is equal to or greater than that in N13, the lesion is totally postganglionic. N9 is normal and N13 is abnormal in pure preganglionic lesions. In mixed lesions N13 is more affected than N9 and the degree of both preganglionic and postganglionic involvement may be estimated from the values. The evaluation of the somatosensory evoked potential is felt to be the most accurate tool for addressing the issue of preganglionic and postganglionic involvement. Accurate assessment is critical because of recent advances in the surgical repair of postganglionic plexus lesions.

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Universal Contoured Cushions for Wheelchair-Bound Patients

THE PRESENT-DAY conventional wheelchair provides little in the way of body support or prevention of soft tissue trauma for a person who has lost sensory feedback or motor function. A new wheelchair seat cushion designated as a Veterans Administration spinal injury orthosis for paraplegics (VASIO-P) has been developed that reduces the ischemia-producing forces and redistributes them to the more tolerant areas of the posterior thighs and lateral gluteal muscles. The cushion is made of foam materials and designed to stabilize the pelvis and promote spinal-pelvic alignment. Pressure measurements were done of 81 persons while seated on the cushion in their own wheelchair. The cushion was effective in reducing pressures to tolerant levels for 65 of them. The cushion was more effective (89% versus 57%) for persons without certain skeletal deformities (pelvic obliquity, bony resections). Of the respondents using the cushion, 83% reported that they preferred it to their previous cushions, with the most commonly cited reasons being improved posture, balance and comfort. This study has shown the cushion to be a preferred alternative to other commercially available wheelchair cushions.

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Perkash I, Pasillas R, Politi D, et al: Seating systems for body support and prevention of tissue trauma. Bull Prosthet Res 1981 Spring; 18:126-127

Heterotopic Ossification in Cases of Head Injury

HETEROTOPIC OSSIFICATION is a frequent sequela of central nervous system injury. It is commonly encountered in cases of spinal cord injury, head injury, cerebrovascular accident and burns. Unlike myositis ossificans traumatica (the formation of calcification and heterotopic bone as a result of local trauma), neurogenic heterotopic ossification is not associated with local trauma. The incidence of heterotopic ossification in patients with a head injury has been reported to be between 11% and 70%.

Factors such as length of coma, depth of coma, level of spasticity and duration of immobility apparently account for the discrepancy in incidence. There is a possibility that osseous trauma may be associated with an increased incidence of heterotopic ossification distal to the trauma site, but this may, in fact, be due to the extent of the original cerebral injury.

The onset of heterotopic ossification may be as early as two weeks postinjury and patients remain susceptible to its onset through the first nine months after injury. Triple-phase bone scan studies clearly show increased local vascularization in a site where heterotopic bone ultimately develops. Although the alkaline phosphatase level is raised in the presence of calcium deposition, the development of heterotopic ossification precedes the elevation of serum alkaline phosphatase. Conventional x-ray studies are normal in the earliest stages of developing ossification. The most consistently reliable diagnostic indicator is a bone scan that shows increased uptake; the earliest changes are shown by triple-phase bone scan studies.

Although the hip appears to be the most common site of heterotopic ossification formation, it occurs with almost equal frequency in the upper extremities and at both the elbow and the shoulder from craniocerebral injury.

In the phase of increased local blood flow, the involved extremity may present with swelling, localized and systemic temperature elevation and rubor. The

differential diagnosis at this stage includes thrombophlebitis. Every effort should be made to preserve as much motion as possible in a joint that shows early heterotopic ossification and, thus, passive range of motion is essential. In the early phases, when joint mobility is threatened, manipulation may be considered. At the first sign of heterotopic ossification, etidronate disodium therapy should be initiated because in some 16% of cases of heterotopic ossification, joint ankylosis will develop. In some patients treated with etidronate disodium, heterotopic ossification will continue to develop and it appears that a dosage of 20 mg per kg of body weight and a longer period of treatment may be necessary.

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Rehabilitation of Stroke Patients Who Have Associated Cardiac Disease

THE POTENTIAL FOR A combination of myocardial infarction and cerebrovascular accident, or stroke, to occur following a cardiac surgical procedure is well known. The rehabilitation of such patients with this combined problem must proceed with care so that the stroke rehabilitation program does not exceed a patient's exercise tolerance relative to the coexisting heart disease. This problem is illustrated by the fact that a hemiplegic patient who ambulates without bracing uses about 65% more energy in ambulating than does a normal person walking at the same speed. Similarly, a hemiplegic person uses up to 35% more energy in climbing stairs than does a normal person.

Recently a program has been designed for managing patients with combined cerebrovascular and cardiac diseases using principles of both stroke and cardiac rehabilitation.

This program proceeds in a stepwise fashion through steps 1 to 14 much as in a typical cardiac rehabilitation program. Although in the traditional cardiac program a patient advances one step a day, each step may take one or several days in a program for the combined disorder. The key to the combined program is careful control of energy expenditure varying from 1.12 METS (metabolic equivalent; 3.5 ml of oxygen per kilogram per minute) at step 1 to 9 METS at step 14. This planned energy expenditure is in keeping with standards for cardiac rehabilitation. Within the program as outlined, there are specific suggestions for physical and occupational therapy and ward activities.

Further specific guidelines include allowing a maximum heart rate of 110 a minute or less in the early steps and 120 a minute or less at step 14. Data for calculating maximal allowable heart rates by percent increase are also available as are further medical precautions such as ceasing activity with angina, and getting electrocardiograms and Holter monitor studies. As with routine cardiac rehabilitation, adequate warm-up and cool-down periods are necessary.

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Staged Treatment of Spasticity

SPASTICITY IS PRESENT in central nervous system diseases such as stroke, spinal cord injury and multiple sclerosis. In patients with lifelong disability, the dangers of adverse effects and addiction are so significant that five stages of treatment have recently become established: (1) reassurance and education, (2) prevention and treatment of contributing causes, (3) physical therapy, (4) medication and (5) blocks and surgical procedures.

During the first stage, a physician needs to reassure and educate the patient and family about the following: spasticity retards muscle atrophy and decreases the chances of phlebitis occurring; an increase in spasticity is an invaluable diagnostic clue when patients cannot feel pain with the occurrence of lithiasis, decubiti, appendicitis or fractures; when spasticity is removed, patients may lose erections, bowel and bladder control, and may suffer further impairments in ambulation or transfers.

The second stage is that of amelioration of inflammation, infection, anxiety and agitation that may aggravate the spasticity. Support, relaxation and cognitive therapy are preferable to psychotropic drugs, many of which have hypotensive, anticholinergic, sedative or habituating side effects.

The third stage involves physical therapy (reducing contractures), functional training (moving the metatarsal heads off wheelchair pedals stops clonus) and physical modalities (heat at 38°C [100°F], ice to 15°C [59°F]).

Once the first three stages have been implemented, additional measures should be taken only when spasticity interferes with function or hygiene or produces significant discomfort.

The fourth stage involves medication. Baclofen, which inhibits reflexes in the spinal cord, is the first-line drug, except in patients who have a history of hallucinations or seizures. Dantrolene sodium, which has a direct effect on muscle, is the second-line drug; it occasionally produces a hepatotoxic reaction. Diazepam is the third drug. Its effectiveness is correlated in large measure with a sedative effect. It may produce urinary retention, respiratory depression and addiction. If an adequate response is not obtained with a single drug, two may be tried together. All three drugs taken simultaneously usually produce unacceptable side effects.

The fifth stage involves chemical neurolysis and surgical procedures. Motor point and nerve blocks are

the simplest and safest methods of treating focal spasticity such as ankle clonus and adductor spasticity. Other ablative procedures are drastic and preclude any hope of future recovery.

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Nuclear Magnetic Resonance Spectroscopy for Diagnosis of McArdle's Disease

MUSCLE DISCOMFORT, pain and even muscle cramps are symptoms *occasionally* experienced by everyone following unaccustomed exercise. Because this is such a common experience, these symptoms frequently receive little attention in routine history taking and physical examination. In a healthy person, these symptoms only occur following strenuous exercise. Patients with a metabolic disorder that interferes with muscle energy supply mechanisms have pains and cramps with even moderate activity. Common diagnoses are laziness, malingering or psychosomatic illness. For example, patients who have McArdle's disease usually have symptoms from childhood, but this disorder is rarely diagnosed until the symptoms become severe, usually during the fourth or fifth decade. As children, if they try to "keep up with their peers" they experience pain and on occasion will have pigment in their urine. As adults, because of the muscle pain they are unable to continue at jobs that require a mild or moderate amount of physical activity for more than brief periods. By all traditional methods for physical examination, they appear healthy and normal, a fact that usually results in a diagnosis of malingering or psychosomatic illness. With aging, the altered muscle function becomes more obvious and a diagnosis may finally be made. In the meantime, a patient may even undergo unneeded laminectomy in the hope that limb "claudicatory" symptoms can be relieved.

McArdle's disease is diagnosed by electromyographic confirmation of electrical silence during muscle contracture, absence of ability to raise the serum lactate level with ischemic exercise, histochemical evidence of glycogen accumulation (glycogen storage disease) and biochemical assays to confirm the absence of phosphorylase activity on tissue taken at muscle biopsy. All of these methods are invasive to a minor or a major degree.

A new *noninvasive* method is now available for studying the energetics of muscle function. The technique is topical nuclear magnetic resonance spectroscopy (no relationship to nuclear magnetic resonance imaging). This technique is of proved value in confirming the diagnosis of McArdle's disease and, based on our recent experience, has potential for identifying carriers of this disorder. The procedure evaluates consumption and alteration of the various high-energy phosphagens noninvasively while muscle activity is occurring. Therefore, this technique has the potential to identify cases of other enzymatic disorders that relate to energetics of muscle function. Topically applied nuclear magnetic resonance will not replace the standard diagnostic procedures. However, it significantly expands the ability to noninvasively screen patients with signs and symptoms suggesting a metabolic disorder of muscle function. Although not yet widely available, it is an established tool in the evaluation of muscle disorders.

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Editorials

Thoughts on Personal Health Maintenance

As the coming crunch of not enough dollars for health care begins to hit home for patients and for society alike, it appears certain that more attention will be given to maintaining personal health. This will be in the economic interest of all concerned. Avoiding illness, injury or emotional disturbance has always been the aim of what we have been calling prevention or preventive medicine, but it seems likely that these efforts will be even higher on one's personal or even the national agenda in the quite foreseeable future.

It is relatively easy to list the many things that can and should be done to prevent disease, disability or postpone death, or to improve health so that one simply feels better. Some of the measures are strictly medical such as immunizations against certain diseases; others pertain to public, occupational, environmental or industrial health; still others relate to life-styles or habits such as cigarette smoking, alcohol or other substance abuse, sexual promiscuity or driving unsafely on the streets or highways; and then there are some things persons can do to enhance their own health and well-being—eat wisely, control weight, exercise, rest, relax, avoid stress and so on. If one is already ill, or disabled, or even facing death, there are always other things one can do to avoid further discomfort, disability or unnecessary expense and even to enhance one's well-being under the circumstances.

Advocates of personal health measures or social initiatives for health often seem to assume that everyone wants above all to be healthy and to live a long time, and therefore will logically do everything they can to achieve these objectives. From this assumption it is an easy step to a paternalistic attitude and approach (which young people especially are wont to reject), and then to disillusion and disappointment when large numbers of people and large segments of society simply do not do as health maintenance advocates believe they should, except where legal compulsion has been introduced to make them do so. The reality is that while health may be given lots of lip service, it is probably not as far up on many a personal or social agenda as we would like to think it is.

Part of the problem may be that prevention seems to have something of a negative connotation. If something is prevented, then it doesn't happen and then there is no evidence that anything was accomplished. Personal health maintenance may seem more positive. At least one is doing something that can be seen and understood. But another part of the problem may be much more profound. It is human nature to take chances. It is by taking risks that humans have achieved. It is by no means unusual for persons to risk health, or even life, for some cause they believe to be important, or even just for the thrill of it. This is unlikely to change and, programmed as we are, it probably cannot change. But this very human characteristic can make a mockery of health maintenance and it seldom reckons the cost either in dollars or in health.

Personal health maintenance emerges as a very complex subject. Increasingly there just is not enough money for health care and surely this will give the subject a new importance. But it will not be enough simply to try to prevent specific diseases, injuries or emotional stresses, or even to promote what we believe to be good for health, although all of this is important to do. Just as in good patient care, it will be necessary to work with a whole person and the whole of society if there is to be much or lasting effect. Economic pressure may be one stimulus to do this, but the challenge to physicians and the medical profession to promote personal health maintenance will require our best professional skills and our best efforts. Now the time has come to put it high on our own professional agenda. MSMW

Diagnosing Brain Death

I grew unsure as I did lie
if dead I were or still to die.

SIR CHARLES S. SHERRINGTON, 1906
The Assaying of Brabantius

When the outcome of modern technologic intensive care is brain death, a physician must consider how long to persist with life-supporting measures. The traditional concept of death based on the close interdependence of function of brain, heart and lungs does not hold when medical technology separates the termination of these functions.

The medical profession as a whole has accepted, in such cases, a brain-centered definition of death. There is general agreement that death of the brain is an appropriate determination of death of a human being and that once this has occurred, further artificial support is fruitless and should be withdrawn. The concept also seems to be accepted by society at large and has been legally sanctioned in many states. For an individual physician, however, the main, immediate problem is whether he or she can accurately distinguish brain dead subjects from other comatose patients who have a chance of even partial recovery.

Pitts in this issue reviews the clinical criteria in use at San Francisco General Hospital Medical Center; several committees have proposed similar criteria.[1] In essence, brain death is present when there is no clinically discernible evidence of any brain function for an extended period, and when the loss of brain function is the result of irreversible structural damage.

The clinical diagnosis of brain death generally is not

difficult nor subject to error if the criteria outlined by Pitts and others are followed rigorously. Nevertheless, recovery has been alleged to occur in patients who were thought to be brain dead but, in fact, were not. A review of such cases shows that in each instance the clinical criteria were not satisfied. We do not know of a single, medically reported case in which the criteria of brain death were met and yet the patient survived.

The validity of the clinical criteria for brain death has been confirmed in two ways: first, by determining the outcome in patients whose ventilatory support was continued after brain death had been diagnosed, and, second, by analyzing the early clinical features of patients who have survived a period of deep coma (not induced by sedative drugs) to find out whether any of them might have been mistakenly diagnosed as brain dead. The consequences of continued ventilatory support in brain dead subjects have been established. The largest series is that of Jennett and co-workers[2] in which 326 patients with brain death from head injuries received continued support, yet all suffered cardiac arrest within hours to days after the diagnosis.

In our series of 500 patients in coma not due to trauma or drug intoxication, there were 121 survivors one month after the onset of coma.[3] None of these survivors, even in their worst state, would ever have been diagnosed as brain dead. Jennett and colleagues reached the same conclusion after analyzing the clinical data from more than 1,000 survivors of severe head trauma.[2]

It is our view based on the foregoing data that the clinical criteria are reliable so that, when properly applied, they will never lead to the diagnosis of death in a patient who might survive. Nevertheless, the diagnosis of brain death carries a heavy responsibility and some medical centers have found it useful to use supplementary tests, such as electroencephalography, to provide verifiable support to the clinical evaluation. We believe that instruments can never replace the thoughtfulness, experience and thoroughness of a capable physician as a guarantor of the accuracy of a diagnosis of brain death. Therefore, we believe each hospital should designate several experienced and appropriately trained physicians who would be responsible for establishing and certifying the presence of brain death.

Failure to establish hospital guidelines and procedures inevitably makes a diagnosis of brain death "extraordinary," as documented in the report of Tyler and Roberson. The lack of impact of brain death legislation on medical practice, which they reported, also reflects the fact that in most states, even in those with brain death statutes, brain death remains a permissible rather than a mandatory definition of death. In view of the overwhelming evidence that physicians can now recognize brain death within a few hours of brain injury, we believe that it is unethical to indefinitely support patients who have complete and unrecoverable brain damage. A greater appreciation by physicians and by society at large of the logical consequences of diagnosing brain death would prevent unnecessary therapeutic and diagnostic procedures and would increase the number of viable organs available for donation.

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Of Third Parties and Patient Care

It is no secret that America now has the finest and best medical care the world has ever seen. It is also no secret that its expense has become a problem for all concerned. Those who must pay the ever-increasing costs have rebelled, and are demanding that these costs be controlled or even reduced. It is significant that those who are making these demands are not those who provide or receive the care, and indeed sometimes they do not seem overly concerned with what effects cost reductions might have upon the availability of needed care or services. They are third parties, somewhat remote from the human and professional aspects of medical care—that is, doctors, patients and the human and professional interactions that take place between them. For this reason, their interventions, aimed primarily at reducing costs, often seem out of touch or insensitive to what health care is all about and indeed more than once these interventions have wreaked havoc in our health care system. How did all of this happen and what, if anything, can physicians do about it?

The health care costs that are now deemed to be unacceptable have been rising and rising for some time. The reason is success—the medical profession's success in developing and applying unprecedented advances in medical science, and society's success in making substantial progress in applying the social principle of equal access to mainstream health care for all. These successes include new services and technology that have become available (coronary care units and coronary bypass operations are examples); a greater number of people living to more advanced ages who require more care (which has now threatened the fiscal solvency of the Medicare program); a substantial increase in the number of physicians and other health professionals (mandated by society to make possible more health care for more people); a massive involvement by third parties, both public and private, in financing the delivery of health care, which in turn has spawned much costly legislative, regulatory, administrative and judicial rules and laws—and this is not to mention the great number of expensive tort and other court actions that have been brought against doctors and others in the health care system in recent years. All of this has had the effect of bringing yet other kinds of third parties

into the health care equation. And most recently, and paradoxically in the name of cost containment, profit making from health care has been blessed as a good thing, as has open competition and costly marketing of health care services. Altogether it is little wonder that health care costs have been rising.

It is more than obvious that these are times of increasing third party involvement and dominance in health care, and that the number and kinds of these third parties are expanding in both the public and private sectors. One may recall that third parties are called third parties because they are outside the two party doctor-patient interaction that is the essence of patient care, and yet in one way or another they impinge upon it. Third parties to health care are to be found in business, industry, labor, the legal profession, legislative bodies, government bureaucracies and even the courts. But the emphasis of most of them is on dollars, the dollars to be saved or earned in health care. Health care is beginning to be regarded by many of them as an inert commodity to be bought, sold, bartered or exploited for economic gain. While this array of third parties is indeed formidable it remains a fact that they are all peripheral to the central action in health care and often are relatively insensitive to what is going on there and to what is needed. They seem often to pay relatively little heed to how physicians must work, caring for persons who are ill, injured or emotionally disturbed, or to what occurs in the very personal interactions in patient care. The health care "commodity," if indeed it is that, is a living, personal and very human affair whose humanity will have to be recognized as much as its costly technology if we are to continue to have the finest and best medical care in the world.

What can physicians and the medical profession do? Somehow we must see to it that the world's best medical care does survive and continue to prevail in what sometimes seems like an almost insane health care environment. It would seem that the key to what physicians and the profession should do lies in expanding and promoting the concept of the doctor-patient relationship. Physicians have always been concerned with what is best for their patients and collectively the medical profession has always been concerned with what is best for the public health. What is needed now is for physicians to become active and recognized advocates and ombudsmen for their patients in the individual health care situations and for the profession to be the recognized advocate and ombudsman for all patients and for all health care in the broader social, economic and political arenas of society as a whole. Someone must take care of patients' interests and speak out authoritatively in their behalf. Third parties are inherently not able to do this. To the extent individual physicians and the profession do so they will be fulfilling an ancient professional responsibility. To the extent their advocacy is successful and recognized by all concerned, they may expect patients and the public to respond, and in turn speak out and give needed support to physicians and to the profession in what for some time is likely to be an increasingly hostile environment for health care.

When the dust finally settles, and if our goal has been accomplished successfully, the physician-patient relationship should have achieved its finest hour, and Americans should still have the best health care in the world.

MSMW

Cardiomyopathy in Diabetic Patients

It is estimated that more than 4 million Americans have coronary artery disease and about 20% of these have associated hyperglycemia (or diabetes). Heart disease is the leading cause of death in the United States, with more than 700,000 deaths each year and 75% of these being due to ischemia. Approximately 5 million Americans have known diabetes and it is estimated that it may be undiagnosed or may eventually develop in another 5 million. Although diabetes is officially ranked by the National Center for Health Statistics as the seventh leading cause of death in the United States, the National Commission on Diabetes has considered diabetes and its complications as the third leading fatal disease category.[1]

Elsewhere in this issue Kereiakes and associates present an excellent review of heart disease in diabetic patients, incorporating much new information. They emphasize the significance of coronary artery disease in the diabetic population and discuss other topics including insulin and myocardial metabolism, diabetic cardiomyopathy and autonomic dysfunction.

Extramural atherosclerotic coronary artery disease has become the most important single cause of death among patients with diabetes and contributes significantly to the morbidity associated with diabetes. Nevertheless, during the past decade there has emerged an increasing amount of epidemiologic, clinical and experimental evidence that supports the concept that a specific cardiomyopathy in diabetic patients causes congestive heart failure.

In the Framingham study the incidence of congestive heart failure among diabetic patients was higher than among nondiabetic cohorts.[2] This excessive risk appeared to be independent of atherogenic coronary artery disease and hypertension, suggesting that some form of cardiomyopathy is associated with diabetes.

Johnson and colleagues,[3] however, believe that the great majority of diabetic patients with heart failure have what they term the cardiomyopathic syndrome due to coronary artery disease with multiple areas of infarction, whether or not clinical clues to the presence of coronary artery disease exist. They consider that the existence of a unique cardiomyopathy of diabetes—one that is unrelated to coronary artery disease—is unproved.

Also to be considered as a possible cause of cardiomyopathy in diabetic patients is the occurrence coin-

cidentally of idiopathic congestive (dilated) cardiomyopathy. A subgroup in this category are the diabetic patients with alcoholic cardiomyopathy.

Even excluding diabetic patients with the so-called cardiomyopathic syndrome due to coronary artery disease and coincidental cases of idiopathic cardiomyopathy, there still appears to be a population of diabetic patients with myocardial dysfunction who have been considered to have a specific diabetic cardiomyopathy. This latter syndrome has been variously attributed to small (intramural) coronary artery disease, microvascular (capillary) disease, interstitial accumulation of collagen and glycoprotein, or to cardiac metabolic abnormalities.

The concept of small vessel disease as a cause of cardiomyopathy in patients with diabetes has been advanced by several investigators. It should be emphasized, however, that only those studies in which the presence of significant extramural coronary artery disease has been carefully excluded (either by coronary arteriography or by autopsy) can be used in support of this thesis.

Hamby and co-workers,[4] in a study of nonhypertensive diabetic patients who had pronounced cardiac enlargement but no extramural coronary artery disease, described changes in the small intramural coronary arteries consisting of endothelial proliferation and focal perivascular and interstitial fibrosis. Other workers have also documented small vessel disease in diabetic patients with cardiomyopathy in the absence of significant extramural coronary artery disease.[5-7]

Ledet and Lundbaek[8] have reported that the smaller intramural arteries from diabetic patients are more frequently periodic-acid Schiff (PAS)-positive than those in nondiabetic persons. They also noted more connective tissue in the heart muscle of insulin-dependent diabetic patients than in nondiabetics and an increased number of cells in the tunica media of arterioles in diabetic patients.

Although Crall and Roberts[9] found occasional mild fibrous proliferation of intima and increased frequency of PAS-positive deposits in the media of some intramural coronary arteries in insulin-dependent diabetic patients, they considered these abnormalities to be minor and of no functional or clinical significance. Still other workers have failed to document any small vessel disease in diabetic patients with cardiomyopathy.[10]

The capillary microcirculation in diabetic hearts has been recently evaluated. Fischer and co-workers[11] described an increase in the thickness of capillary basal lamina in human diabetic myocardium. Factor and associates[12] in a significant study identified saccular and fusiform capillary microaneurysms in the hearts of several diabetic patients.

Factor and co-workers[13] have described the occurrence of cardiomyopathy in hypertensive diabetic patients who do not have significant extramural coronary artery disease. A similar cardiomyopathy has also been produced in hypertensive diabetic rats.[14] These investigators believe that hypertension has an adverse effect on diabetic myocardium, leading to focal interstitial and replacement fibrosis with associated glycoprotein deposition.[15] These changes could not be correlated with small intramyocardial vessel disease but were thought to be associated with alterations in the microcirculation, including focal constriction of vessels, microaneurysms, increased perivascular mast cells and increased capillary permeability.[15]

Regan and associates[16] have shown that certain diabetic patients who have cardiac symptoms but no occlusive coronary artery disease have significant left ventricular hemodynamic abnormalities consistent with a decrease in diastolic compliance, perhaps attributable to the interstitial deposition of PAS-positive material (glycoprotein) and collagen. In addition, they found an increase in myocardial triglyceride and cholesterol concentrations and concluded that a diffuse extravascular abnormality may be a basis for cardiomyopathic features in diabetes.

Ultrastructural changes in diabetic cardiomyopathy have recently been documented in experimental animals. These include damage to the ventricular myocytes and intramural arteries and capillaries[17] and interstitial accumulation of collagen, basement membrane material, focal replacement fibrosis and cellular hypertrophy.[18]

Finally, various metabolic and functional abnormalities have also been proposed to account for myocardial dysfunction in the absence of significant coronary artery disease.[19] These include reduced adrenergic-receptor binding sites,[20] insulin deficiency[21] and reduced myosin adenosine triphosphatase and serum thyroid hormone levels.[22,23]

In summary, although many unanswered questions concerning diabetic cardiomyopathy exist, there now appears to be adequate evidence to confirm its occurrence in certain diabetic patients who have insufficient extramural coronary artery disease to account for their myocardial dysfunction.

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Case Reports

Cushing's Syndrome in a Patient With Suppressible Hypercortisolism and an Empty Sella

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THE INCIDENTAL FINDING of an empty sella turcica is common even in asymptomatic patients.[1] To date, there have been only three reports of patients with hypercortisolism, elevated plasma adrenocorticotropic hormone (ACTH) level, Cushing's disease and an empty sella.[2-4] In two of these patients,[2,3] a small pituitary adenoma was found at operation in an otherwise empty sella. The third patient[4] did not have a pituitary surgical procedure. In this report, the patient presented with cushingoid features, and partial pituitary hypofunction, an empty sella and an inappropriately elevated plasma ACTH level with partially suppressible hypercortisolism were recorded. Surgical exploration of the pituitary fossa, however, failed to show a discrete adenoma. A small posterior rim of intrasellar tissue was found that contained nests of abnormal basophils. No ectopic source for ACTH could be identified. A pituitary surgical procedure was not successful in controlling the patient's disease but she did respond to a combination of aminoglutethimide and cyproheptadine hydrochloride.

Report of a Case

The patient, a 60-year-old obese Korean woman, had hypertension dating to 1976, treated with salt restriction, thiazides and β-blockers. In 1981 she gained 11 kg (25 lb) in weight in a year, and an increasingly round and pigmented facies developed. The patient first presented to the University Hospital (Seattle) in February 1982 because of increasing shortness of breath and abdominal and back pain. She had mild facial hirsutism, acne, central adiposity, a small buffalo hump and hyperpigmentation over the dorsum of her hands and fingers. Despite blood pressures of 140 to 180/100 to 120 mm of mercury, her fundi were normal and an electrocardiogram did not show evidence of left ventricular hypertrophy or strain. The patient's blood pressure was difficult to control on increasing doses of diuretic, β-blocker and, eventually, minoxidil.

An overnight suppression test with 2 mg of dexamethasone resulted in an 8 AM serum cortisol level of 9μg per dl (normal less than 5). A plasma ACTH level was 80 pg per ml (normal less than 80) and 24-hour urinary 17-hydroxycorticosteroid excretion was 41 mg (normal 2.5 to 10). While she was taking dexamethasone (0.5 mg four times a day for two days) her 8 AM serum cortisol level fell from 43 μg per dl to 27 μg per dl and her 24-hour urinary 17-hydroxycorticosteroid excretion was 32 mg. High-dose dexamethasone (2.0 mg four times a day for two days) resulted in a further decrease of her urinary 17-hydroxycorticosteroid excretion to 26 mg per 24 hours. Visual fields were normal. Tomograms showed the sella turcica to be normal in size and shape, but the bones were demineralized. Computed tomography (CT) of the head (Figure 1) showed low density in the sella turcica with the exception of a posterior rim of soft tissue. Metrizamide enhancement (Figure 2) showed an empty sella with a small mass at the base of the sella.* Computed tomography of the abdomen showed both adrenal glands enlarged but otherwise there were no abnormalities. Spine films showed generalized mineral loss with compression fractures of T-11 and L-1. Chest x-ray films showed an elevated right hemidiaphragm and no mass lesions and suggested the presence of generous amounts of fat in the mediastinum.

Additional endocrine testing yielded the following values: plasma luteinizing hormone, 6 mIU per ml (premenopausal 4 to 30) despite her postmenopausal state; plasma follicle-stimulating hormone, 4 mIU per ml; serum estradiol, 29 pg per ml. A serum prolactin level (30 ng per ml) was slightly raised (normal 0 to 25). Tests of thyroid function showed no abnormalities: thyroxine, 5.1μg per dl (normal 4.1 to 11.3); triiodothyronine resin uptake, 46% (normal 33 to 45); thyroid-stimulating hormone, 1.9 μIU per ml (normal 0 to 6.5). Urinary excretion of 5-hydroxyindoleacetic acid was 6.3 mg per 24 hours (normal less than 10.0).

Because the patient appeared to have pituitary-dependent Cushing's syndrome and review of the literature suggested that even in the case of an empty sella, adenomas could usually be found in such patients, in June 1982, she underwent a transsphenoidal exploration of the pituitary fossa. A small amount of abnormal-appearing fluid was aspirated from the fossa. Multiple biopsy specimens were obtained from a small rim of fibrous-appearing tissue at the base of the sella. The

(Lipkin EW, Fujimoto WY: Cushing's syndrome in a patient with suppressible hypercortisolism and an empty sella. West J Med 1984 Apr; 140:613-615)

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Submitted, revised, October 3, 1983.

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*Douglas Stewart, MD, Department of Cardiology, was involved in various aspects of the workup and management of this patient, and computed tomography and reconstructions were provided by Nicole Bolander, MD, Department of Radiology.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CT = computed tomography

sella was otherwise empty of tissue.* Histologic examination showed a large amount of fibrous tissue and nests of abnormal basophilic cells interspersed with occasional nests of normal-appearing acidophilic cells. The basophilic cells had large amounts of granulated cytoplasm and frequent central vacuolization with displacement and deformation of the nucleus (Crooke's changes). She remained persistently cushingoid and hypertensive and easy bruisability developed as well as generalized muscle weakness of a proximal distribution. Several new vertebral compression fractures developed at T-12 and L-2 through L-5. Follow-up serum cortisol and ACTH levels were 31 μg per dl (4 PM) and 71 pg per ml, respectively, in July 1982. Bilateral adrenalectomy was considered as a treatment option at this point but because of the patient's obesity and poorly controlled hypertension, the procedure was deferred. Unfortunately, a breast abscess developed that did not respond to local incision, drainage and antibiotics, requiring debridement under general anesthesia. Postoperatively she had high-output cardiac failure and hypoventilation. It was elected to institute treatment of her Cushing's disease (see Figure 3) with aminoglutethimide, cyproheptadine and pituitary irradiation with the hope of decreasing the morbidity associated with her cushingoid state and facilitating her postoperative recovery. Her serum cortisol level fell from 68 μg per dl to 29.5 μg per dl but the patient died in September 1982, several days after an unexplained respiratory arrest. A postmortem examination was not done.

Discussion

Of patients presenting with pituitary hyperfunction and an empty sella, most have coexisting prolactinomas or growth hormone-secreting tumors.[5-10] A most unusual syndrome of elevated plasma ACTH level in the presence of an empty sella, normal cortisol dynamics and no cushingoid features has been reported in two patients.[11,12] In one of these two cases, gel filtration chromatography showed nearly all of the immunoreactive ACTH to be a large-molecular-weight form, which the authors speculated to be of reduced biologic activity. Another unusual case of an elevated, non-suppressible plasma ACTH level and an empty sella has been reported in a patient with Addison's disease who remained hyperpigmented despite adequate glucocorticoid replacement.[13] To date, there have been only three cases reported of patients with hypercortisolism, elevated plasma ACTH level, Cushing's disease and an empty sella.[2-4] In two of these patients, a small pituitary adenoma was identified at operation in an otherwise empty sella, while in the third pituitary sella exploration was not done.

The present case is notable in several respects. On the one hand, this is one of only four reported cases of Cushing's disease and an empty sella. In contrast to the previous reports in which pituitary surgical pro-

*The surgical procedure was carried out by William Kelly, MD, Department of Neurosurgery, and the histologic studies were done by Cheng Mei Shaw, MD, Department of Pathology.

Figure 1.—Computed tomography of the head with contrast (diatrizoate meglumine) enhancement. Shown is a lateral computer reconstruction of the sellar area. The **curved arrow** points to the hypodense empty sella containing a small posterior rim of tissue (**straight arrow**).

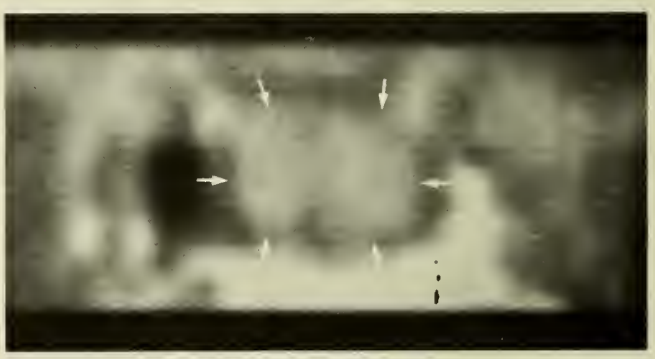

Figure 2—Computed tomography of the head with intrathecal administration of metrizamide. Shown is a coronal computer reconstruction of the sellar area. Metrizamide (hyperdense area outlined by **arrows**) completely fills the sella, confirming the presence of an empty sella. The hypodense area to the left is a pneumatized sphenoid sinus.

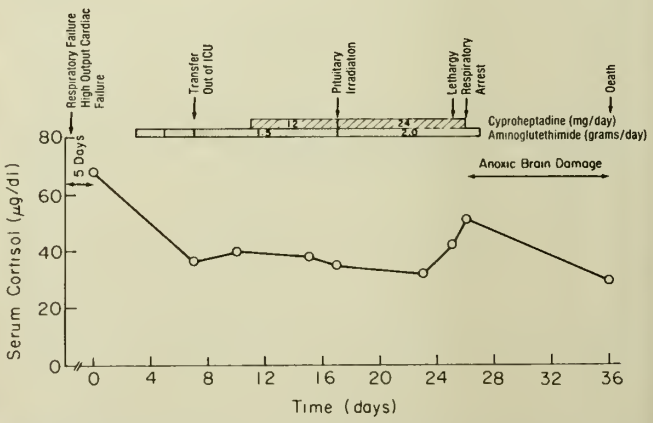

Figure 3.—A summary of the biochemical response to treatment as assessed by serum cortisol levels in the patient during her final hospital stay. Major clinical developments and therapeutic interventions are indicated. ICU = intensive care unit.

cedure was done, however, the small amount of pituitary tissue in the otherwise empty sella had basophilic hyperplasia and no adenoma. In addition, partial pituitary hypofunction is suggested by plasma gonadotropin levels that were inappropriately low for her postmenopausal state. Thyroid function was normal. Several management issues arose during the course of this patient's illness that deserve comment. Selective venous catheterization would have been helpful in establishing the pituitary as the source of inappropriate ACTH production. In a case of pituitary-dependent Cushing's and an empty sella, it is probably still warranted to surgically explore the pituitary fossa for a possible adenoma. Bilateral adrenalectomy remains, however, a reasonable treatment alternative.

The question of whether this patient had Cushing's disease or Cushing's syndrome on another basis cannot ultimately be settled without a postmortem examination. The weight of the evidence suggests a pituitary basis. The factors supporting a primary pituitary aberration are the inappropriate rise in the ACTH level (though still within the normal range) in the presence of extreme hypercortisolism and its partial suppressibility. Other possible causes for Cushing's syndrome appear to be reasonably excluded. Documentation by CT scan of enlargement of both adrenal glands rules out a unilateral adrenocortical adenoma as the source of this patient's hypercortisolism. An ectopic source for ACTH is also unlikely for several reasons. The patient's long clinical course (six years), negative findings on a chest x-ray film, normal 24-hour urinary excretion of 5-hydroxyindoleacetic acid and partially suppressible hypercortisolism are inconsistent with an ectopic source for ACTH. Furthermore, the ACTH level in this paraneoplastic syndrome tends to be much higher than occurred in this patient. The failure of high-dose dexamethasone to suppress urinary 17-hydroxycorticosteroid excretion by at least 50% may argue against pituitary-dependent Cushing's disease, but 15% to 30% of these patients fail to suppress to this degree.[14]

This case also has potentially interesting implications concerning the natural history of Cushing's disease. If this patient's primary defect was at the level of the hypothalamus resulting in inappropriate stimulation of the pituitary, this would have caused development of a pituitary adenoma, ACTH hypersecretion and cushingoid features. Infarction of the adenoma may have then occurred, resulting in an empty sella. Of other possible causes of an empty sella, a developmentally incomplete sellar diaphragm cannot be completely excluded, whereas involution of a previously hypertrophied and overstimulated pituitary due to end-organ failure appears highly unlikely.

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Homonymous Hemianopia Due to Cerebral Air Embolism From Central Venous Catheters

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PERCUTANEOUS PLACEMENT of a central venous catheter has become a routine bedside procedure. Immediate mechanical complications include direct trauma to nerves, arteries and pleura and embolization of air or catheter fragments. Delayed complications are primarily infectious and thrombotic in nature.[1,2] The following reports of cases illustrate an unusual complication of central venous catheters—homonymous hemianopia due to cerebral air embolism—and highlight the need to implement precautions to prevent this complication.

Reports of Cases

CASE 1. The patient, a 60-year-old man, was admitted for control of malignant hypertension and unstable angina. Evaluation showed diffuse arteriosclerosis, which included carotid and renal artery disease as well as 70% occlusion of his left anterior descending and right coronary arteries. The patient underwent right carotid endarterectomy in April 1981 and coronary-artery-bypass graft operation three weeks later. Both procedures were uneventful. Five days after the cardiac operation the patient was transferred to the ward with a left subclavian venous catheter in place.

(Kearns PJ Jr, Haulk AA, McDonald TW: Homonymous hemianopia due to cerebral air embolism from central venous catheters. West J Med 1984 Apr; 140:615-617)

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Submitted, revised, June 22, 1983.

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Two hours later, the patient unwittingly disconnected the catheter tubing to walk to the bathroom. He was found standing in the doorway with the central venous catheter disconnected, complaining of shortness of breath and back, shoulder and jaw pain. On physical examination, the patient had a heart rate of 120 per minute, a respiratory rate of 30 and a blood pressure of 200/170 mm of mercury. No blood was noted to escape from the disconnected catheter. He had a left homonymous hemianopia and diminished sensation of the left side of his body; both findings were new. His supine central venous pressure measured 4 cm of water, which remained stable for the next 24 hours. The patient was placed at bed rest and given high-flow oxygen therapy. His blood pressure gradually fell to 130/80 mm of mercury during the first hour and his respirations returned to 20 per minute.

A diagnosis of air embolism from the disconnected catheter was considered. A computed tomogram (CT) of the head done 12 hours after the initial symptoms showed a circumscribed 4-mm air-density lesion (about −400 Hounsfield units) in the right calcarine cortex consistent with an air embolus in the right posterior cerebral artery (Figure 1). This finding correlated well with the patient's symptoms of left homonymous hemianopia and left-sided sensory abnormalities. The patient's sensory deficits totally resolved during the ensuing five days, and the visual field defect improved slightly. A repeat CT scan five days after the initial study showed complete resolution of the air embolus, with a residual area of low attenuation in the right occipital cortex consistent with cerebral infarction. Review of the findings of the physical examination, cardiac catheterization and echocardiogram showed no evidence of ventricular or atrial septal defect or a patent foramen ovale. He was discharged and readmitted eight months later for aortofemoral bypass with renal artery reconstruction. At that time he had only a residual inferior left quadrantanopia.

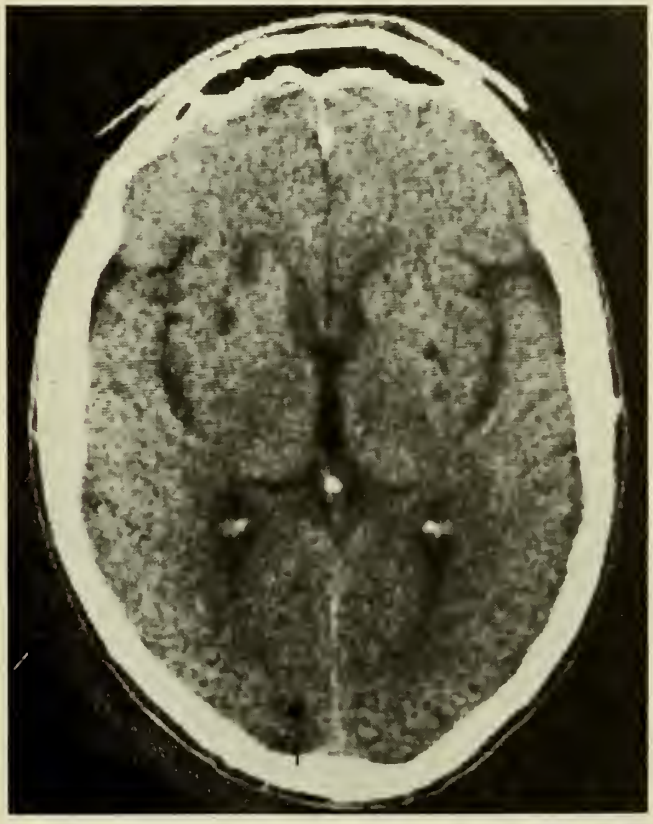

Figure 1.—Computed tomogram of the patient in case 1 obtained 12 hours after the onset of symptoms, showing an air-density lesion **(arrow)**. A repeat scan 5 days later showed resolution of the air-density lesion with a residual area of low attenuation.

CASE 2. The patient, a 63-year-old man with diabetes mellitus and coronary artery disease, was admitted because of bacteremia, cellulitis and staphylococcal abscesses of the left lower extremity. The patient had poor peripheral venous access and required a central venous catheter for intravenous administration of antibiotic therapy. Two days after placement of the catheter, he inadvertently removed the catheter despite stabilization by a suture ligature. A sterile dressing was applied. Within an hour the patient noted decreased vision in his left eye, but he did not report this symptom at that time. A second central venous catheter was placed without incident, and antibiotic therapy was continued. Five days after placement of the second catheter, the patient complained of persistent left eye "blindness" and stated that the onset had occurred at the time of the dislodgement of the first central venous catheter. On physical examination a left homonymous hemianopia was found. A CT scan showed an area of low attenuation in the occipital cortical region consistent with cerebral infarction. Digital subtraction angiography showed no evidence of carotid artery disease. Neither echocardiogram nor cardiac catheterization showed evidence of a mural thrombus or valvular vegetation. A two-week course of antibiotics was completed and the infection resolved. The left homonymous hemianopia was unchanged when the patient was seen a year following the cerebral infarction. The CT scan has remained unchanged.

Discussion

The case of a patient who had a cerebral air embolus from a disconnected central venous catheter with a transient homonymous hemianopia was reported by Menkin and Schwartzman.[3] Postulated mechanisms for the neurologic symptoms following air embolism include obstruction of the outflow tract of the right ventricle with consequent decrease in cardiac output, intense cerebral vasospasm induced by air emboli passing though intracranial vessels and actual occlusion of cerebral vessels by trapped air emboli.[4,5]

The findings of the CT scan in the first patient may be the first clear clinicoanatomic correlation between neurologic symptoms and an air embolus in the brain. In this patient the underlying pathophysiologic feature was obstruction to cerebral blood flow by the air embolus, which caused ischemia and infarction. The timing of the CT scan showed that clinically significant air

TABLE 1.—*Accumulated Experience of Cerebral Air Emboli*

Study, Year	*Patients N**	*Catheter Associated N*	*Neurologic Symptoms (N)*	*Mortality %*
Green and Nemir, 1971[11]	1	1	Blindness (1), paresis	...
Hoshal and Fink, 1969[12]	2	2	Semicoma (1)	...
Ponsky, 1971[6]	1	1	Coma (1), seizures	100
Menkin and Schwartzman, 1973-1974[3]	5	1	Hemianopia (1)	40
Coppa et al, 1976-1980[13]	14	14	Coma, seizure (9), hemiplegia	30
Grace, 1977[14]	2	2	Hemiparesis (2), coma	...
Peters and Armstrong, 1978[5]	2	2	Monoplegia (1)	50
Michel et al, 1982[15]	1	1	Coma (1)	100
Eisenhauer et al, 1982[16]	3	3	Seizure (2)	...
TOTALS	31		19	

*Total number of patients in cited report who had presumed air emboli.

emboli can persist up to 12 hours and are resorbed within five days.

The mechanism by which venous air emboli are delivered to the systemic circulation is controversial. The previously postulated mechanisms presumed obstruction of the outflow tract of the pulmonary artery by air embolism with an increase in the pulmonary artery pressure transmitted to the right atrium. There is subsequent shunting of blood through an existing anatomic defect, such as a patent foramen ovale.[6] Alternative explanations must now be considered because the first patient had a low central venous pressure during the entire period of observation. In addition, neither an atrial septal defect nor a patent foramen ovale could be found. Intrapulmonary, physiologic right-to-left shunts have been found in dogs and in humans.[7] These are presumed to be patent and functional and are of sufficient size to allow passage of air emboli. Butler and Hills showed in dogs that aminophylline and vasodilators "open up" the pulmonary venous-arterial barrier and allow passage of air emboli to the arterial circulation.[8] The appearance of systemic air emboli with normal right-sided pressures in case 1 supports the significance of intrapulmonary shunts in the pathophysiology of the cerebral air embolus.

The neurologic symptoms of these two patients were assumed initially to be due to malignant hypertension, atherosclerotic disease or an idiopathic cause. Because of a high index of suspicion for cerebral air embolism, this diagnosis was confirmed in the first patient, and all other possible causes were excluded in the second patient. In all, 19 cases with the clinical diagnosis of cerebral air embolism due to central venous catheters have been reported, 15 within the past five years (Table 1). Because of the increasing use of central venous catheters for central pressure monitoring, for alimenting, in placing temporary pacemakers and in subclavian catheter dialysis, the incidence of air emboli with neurologic complications is likely to increase. Because these two patients were standing during their episodes, the air embolus followed a predictable route and traveled to the right posterior circulation. As noted by Ohkuda and co-workers,[9] venous air emboli usually do not cause symptoms, possibly because in supine patients the embolus can travel to neurologically silent areas. Because of this and the misconception that significant air emboli cause cardiovascular collapse, many air emboli may go unnoticed.

Because of the unknown incidence of this complication and the increasing use of the procedure, the following precautions are recommended for all central venous catheter placements:

- Follow proper insertion technique[10];
- Use Luer-lock connections to the catheter to avoid disconnection;
- Place suture-ligatures to prevent movement of the catheter, best accomplished with catheters equipped with ligature eyelets.

If these simple precautions are followed, cerebral air embolism should be reduced. When the possibility of air embolism exists, the use of computed tomography for the early diagnosis of cerebral air embolism should expedite the diagnosis and institution of definitive therapy.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Thrombocytopenia in Colorado Tick Fever

To the Editor: I want to point out an important error that appeared in the otherwise excellent article "Successful Treatment of Rocky Mountain 'Spotless' Fever" by Ramsey and Press in January 1984.[1] In the legend comparing Rocky Mountain spotted fever, relapsing fever and Colorado tick fever, the authors indicated that thrombocytopenia is found in Rocky Mountain spotted fever and relapsing fever but not in Colorado tick fever.

In the *Archives of Internal Medicine,* April 1962,[2] I reported a case of thrombocytopenia in Colorado tick fever. Indeed, it was pointed out that this used to be a differentiating point between Rocky Mountain spotted fever and Colorado tick fever. The case I studied was serologically proved to be Colorado tick fever. Definite thrombocytopenia appeared which remitted after recovery from the disease. Indeed, I made the point at the time that thrombocytopenia is probably a regular recurring event in most viral diseases, even usual childhood diseases. Usually one does not do platelet counts unless symptomatic bleeding or petechiae occur. These are not likely to occur unless the platelet count goes below 50,000 per μl but indeed mild to moderate thrombocytopenia probably occurs if it is looked for regularly in most viral diseases. I indicated that it would not be unusual, therefore, to find thrombocytopenia occasionally in Colorado tick fever. Indeed, in my case report thrombocytopenia was substantial. Thrombocytopenia cannot be used as a differential point between Rocky Mountain spotted fever and Colorado tick fever and that implication in Table 1 of the article by Ramsey and Press is, therefore, inaccurate. It should be corrected.

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* * *

Drs Ramsey and Press Reply

To the Editor: We agree with Dr Markovitz that thrombocytopenia may develop in patients with Colorado tick fever. As Dr Markovitz mentions, mild thrombocytopenia has been associated with many viral diseases. However, severe thrombocytopenia has not been a feature of Colorado tick fever except in the case reported by Dr Markovitz. In a series of 228 cases of Colorado tick fever, only one patient had petechiae and only five patients were found to have mild thrombocytopenia.[1] In contrast, severe thrombocytopenia associated with petechiae or purpura has been found more frequently in patients with Rocky Mountain spotted fever and relapsing fever.[2,3]

The table in our case report was designed to provide an outline of the clinical features of tick-borne infections in the western United States. Our intent was to present the characteristic laboratory findings for each infection. Leukopenia is a frequent finding in patients with Colorado tick fever but thrombocytopenia has been reported only rarely. However, we agree with Dr Markovitz that the finding of thrombocytopenia does not eliminate the possibility of Colorado tick fever in a patient with a tick-borne infection.

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Surgical Privileges in a Small Hospital

To the Editor: Hospital (especially surgical) privileges are a significant issue relating to quality of care. As changes in techniques and knowledge occur in medical science and practice, the practice patterns of the individual physicians in the community also change. Assignment of specific privileges based on training, experience and current competence may be a crystal clear issue at the completion of training, but it becomes progressively more turbid with the passage of time to the point of being frankly muddy in a few years.

In my 11½ years in practice in a rural northern

California community, the physician community has expanded from eight family physicians and a part-time radiologist to nine family physicians, two general internists, two general, thoracic and vascular surgeons, two orthopedic surgeons, one anesthesiologist, a full-time radiologist, an ENT specialist, a urologist, a podiatrist and a nurse anesthetist. This expansion of personnel has been accompanied by a change in the medical and surgical case mix, and in the average "level of performance" in the patient care. Some of the older physicians, who were previously quite active in surgery, medicine and obstetrics, have started to refer patients to specialists for care in these areas. As a matter of pride, however, they are reluctant to relinquish hospital privileges for areas in which they choose to refer but in which they nonetheless continue to feel competent. The specialists are concerned, in their turn, about the increasing incompetence of the physicians whose current experience is scant. The younger family physicians view with alarm any move to restrict the privileges of similarly trained physicians in areas where the younger physicians are actively practicing.

Our staff has a sincere commitment to quality of care and a commitment to work together to find solutions to staff governance problems. Long discussions between the advocates of privilege restriction and the advocates of privilege maintenance has resulted in a three stage compromise solution:

- *Stage A*. For a physician who has not done a particular procedure or one of similar and related type for two years (we are on a two-year surveillance schedule), all charts related to such care will be reviewed by a member of the surgery committee to check for complications.
- *Stage B*. If the procedure (or related one) has not been performed for four years, another physician must be present to observe and evaluate the surgeon and report on adequacy of performance to the surgery committee.
- *Stage C*. If the procedure has not been done for six years, a physician with unrestricted (or stage A) privileges must be chosen (or assigned by the chief of surgery) to evaluate surgical performance and report to the surgery committee. The surgery committee has agreed that no one will be granted surgical privileges without agreement to fulfill this evaluator role.

This system is a compromise. No one is satisfied, but everyone can live with it. The surgeon specialists believe that infrequent surgeons should be denied privileges, but they are willing to accept close evaluation of performance as an alternative. The older generalists, who are the infrequent surgeons, do not believe that such supervision is necessary or proper, but since privileges are not being denied, they are reassured. The younger generalists are reassured that they will be evaluated based on skill and competence, not board eligibility.

Not only are we hopeful that this system should work for assuring patients of competent handling by the generalists, but it should function just as impartially in the case of a surgical specialist who may be an infrequent surgeon in one or more areas of his field.

ROGER K. HOWE, MD
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A Good Doctor

To the Editor:

Faces we see, hearts we know not. *Spanish proverb*

Since my graduation from medical school almost 25 years ago, I have interviewed numerous young people who either aspire to become doctors or, having already done so, are competing for a training position or practice opportunity. Experience has taught me the frustrations and occasional mistakes involved in the attempt to measure a "good doctor."

Letters of recommendation and the curriculum vitae are helpful, but far from perfect. I look for signs of high intelligence and excellent health. I search for traits of integrity, discipline, diligence, curiosity, caring and especially personal honor.

The interview begins and ends. I have talked, listened and observed. I now know the applicant, but do I know his or her heart?

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Treatment for Rhus Dermatitis

To the Editor: Many readers may be interested to learn of a treatment for the itch of poison oak (rhus) dermatitis that is inexpensive, not unpleasant, safe and apparently more effective than much conventional therapy. The use of hot soapless showers for this disorder is not mentioned in standard textbooks of allergy or dermatology. After our interest in this technique developed, however, a letter of inquiry was sent to 100 local physicians. Eight of them had found it to be helpful in treating their own rhus dermatitis and three of them had repeatedly recommended it to patients because of its apparent effectiveness. Most primary physicians and dermatologists, however, were unaware of its use.

During previous episodes of rhus dermatitis extending over a 40-year period, I had confirmed many times the marginal relief obtained with topical corticosteroids[1] and had found the side effects that accompanied systemic steroids to be unacceptable to me. It was with great delight, therefore, that a hot shower was found to be followed by several hours completely free of pruitus, and that frequent subsequent showers were each equally effective. After this personal discovery, shower therapy was undertaken seven times during the first 24 hours and less frequently, but as often as required, thereafter. The uncomfortable days and restless nights that had characterized earlier episodes of dermatitis were replaced by predictably undisturbed between-shower intervals during which I was able to feel well and function normally.

Since then, 15 patients with recurrent poison oak

dermatitis have been asked to compare the effectiveness of hot showers with that of 0.1% triamcinolone cream, used as freely and frequently as desired. Some of these patients were also treated with systemic corticosteroids. Showers were taken without soap, by directing "comfortably hot" water onto affected areas until the resulting pleasant sensation had subsided, and any accumulated exudate had been washed away. Each affected area was then patted dry with a towel. All patients reported that hot showers resulted in hours of complete or nearly complete relief from their itch, whereas the topical steroid was of little or no help in this regard. Several patients required reassurance that their therapy could not spread their disease, the appearance of new areas of dermatitis representing the natural history of their disorder.

In none of the patients using the hot shower treatment did secondary infection develop, a frequent complication of conventional therapy. This apparent advantage seemed likely to have resulted from the cleansing action of hot water, the washing away of the exudate which otherwise provided a rich culture medium for bacterial growth and the effective prevention of scratching and rubbing with their attendant trauma and bacterial contamination.

Our experience suggests that this technique is worthy of much more widespread use.

HARRY W. DANIELL, MD
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Ectatic Is Not Tortuous

To the Editor: I read with interest the Medical Progress article "Abdominal Aortic Aneurysms."[1]

I would like to comment on the improper usage of the word "ectatic" as a synonym for "tortuous" or "uncoiled."

Dorland's Illustrated Medical Dictionary defines ectatic as "distended or stretched." This definition applies to the aorta, as well as to the bronchi (bronchiectasis), ureter (ureterectasis), mammary duct (mammary duct ectasia) and so forth.

Descriptions of a normal-caliber aorta as "ectatic," when one really means "tortuous" or "uncoiled" can only lead to confusion.

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Outlawing Boxing

To the Editor: Dr Joseph Elia's statement in "Physicians and Boxing"[1] that if boxing is banned it will go underground will not hold. Boxing flourishes because of the huge pots made available by TV revenues, stadium attendance and the like. Once these are gone so is the financial lure for athletes.

Boxing is legalized brutality. Attempts to sanitize it will fail. The public (no different from the mobs at a Roman coliseum) pays to see the gory battering and knockdown. Anything less is boring and the TV ratings fall. The great majority of youths who are lured into this "sport" by the promise of gold and glamour wind up as brain-damaged wrecks, if not fatalities. Physicians should exert every effort to get this barbarism outlawed. Sweden and Norway have done so[2] and we should follow their lead.

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Do-Not-Resuscitate Orders and the Doctor-Patient Relationship

To the Editor: As a fourth-year medical student who will soon be facing questions of life and death concerning my own patients, I was very dismayed to read the hospital reports on do-not-resuscitate (DNR) orders in the January issue.[1,2]

Unfortunately, I was not surprised.

The articles indicated that house officers are most responsible for no-code orders; indeed, the Portland VA study[2] revealed that interns and residents participated in DNR decisions much more than attending physicians, family members or the patients themselves did.

My own experience has been similar. Decisions to not resuscitate patients whom I have followed have invariably been reached by an intern or resident after a brief discussion with the patient or patient's family. Often, the actual question of "resuscitation" was never raised; instead, the participants would vaguely discuss the patient's prognosis and how he or she might like to die. Rarely was the discussion prolonged or debated. Even more rarely did the attending physician participate. Never was a priest or minister or lawyer or any other kind of counselor involved.

On the positive side, I think that in all the cases there was good reason not to resuscitate—the patient having either an obviously terminal illness or a very long history of hospital care—but I found the decision process perfunctory and demeaning. I certainly do not want to be treated that way when I or one of my parents is old and sick.

Physicians are not philosophers or clerics; yet we are very often in a position to act that way. And while it is not reasonable to assume that we should all be-

Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

come experts in the ethics of resuscitation, I think it is our responsibility to understand its basic questions. We spend a lot of time in medical school and in continuing education learning when and how to work up and treat various presenting signs and symptoms. Should we not also discuss the indications for and against the use of resuscitation techniques?

Most medical schools, including my own, do instruct students in ethics, communication skills and the psychologies of grief and pain as part of our introduction to the "doctor-patient relationship." The problem is that when we hit the wards in our third and fourth years, these issues are largely ignored: the thoughtful and considerate psychiatrists and sociologists are gone, and the academic ward attending physicians, who are always rushing off to their labs or to one more surgery, don't have the time or will to discuss such matters. The final result is that these issues are not only ignored, but that this ignorance becomes transformed—first to indifference and then to avoidance.

I would like to propose a four-week course for fourth-year medical students that would replace part of the preclinical social science curriculum. The purpose of this course would be to review interviewing skills *after* students have interviewed for a year and know what the difficulties are; it would reinvestigate death and dying *after* students have cared for the terminally ill and understand what they and their families are experiencing; it would reexplore ethical issues such as a patient's right to know, the use of ventilators and other extraordinary means, and the determination of code status *after* students have seen these problems arise in real life; it would review the role of preventive medicine and patient education *after* students have examined the "pink puffers" and "blue bloaters," the malnourished and the abused. It does little good to address these issues theoretically if we do not also learn how to think about them and apply them clinically.

And we do need to apply them. In an age when most American physicians are equally competent—and equally expensive—in treating common medical problems, it is our understanding of the interpersonal art of medicine that will set us apart. The combination of greater public knowledge about health matters, severe malpractice suits and physician overpopulation makes it imperative that doctors pay more attention to the doctor-patient and doctor-family relationships. For our patients' benefits and for our own economic and personal integrity, we are going to have to learn to practice what we preach.

At the moment, all I can do is preach. Come July, however, I will start to practice, and I know that I won't be any more comfortable discussing DNR orders with my patients then than I am now. My hope is that experience will teach me how to conscientiously approach these issues, but I have a feeling that experience will only confirm bad habits. Establishing new habits will require new role models and new positive experiences. I think we should start now.

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'Officialese' Versus Plain English

To the Editor: The special article by Stephen Lewis in the January issue on prospective pricing and DRGs[1] is one of the most important articles on the economics of medicine published in the journal in many years. The information is of interest to any practicing physician, in addition to hospital administrators. The history of DRGs and the way they are supposed to work will have a tremendous impact on the way we practice medicine over the next few years. Mr Lewis is to be complimented for his effort.

Unfortunately, Mr Lewis has chosen to write this article in the "official style," not plain English. As a result, it is almost unreadable. Any physician who has read this article in its entirety is either to be complimented or accused of being a masochist. Any physician who is able to understand the content had to translate the article. This is unfortunate. The prospective pricing system and DRGs are too important to be lost in the unnecessary, overly complex prose of "officialese." Mr Lewis would do us all a service if he rewrote the article in plain English. We all need the information he presented.

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Editor's Note

Will this "officialese" not soon be common usage? It seems likely.

MSMW

Topics in Primary Care Medicine

Pressure Sores

THOMAS G. COONEY, MD, *and* JAMES B. REULER, MD, *Portland*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN P. McPHEE, MD
Series' Editors

Pressure sores are a common problem and have a major effect on patient morbidity, mortality, rehabilitation and health care expenditures. A general lack of knowledge or interest in this problem has fostered inadequate preventive care and poor understanding of treatment.

Pressure sores occur most frequently in two populations: patients with spinal cord injuries and elderly patients. Pressure sores develop in 25% to 85% of all patients with spinal cord injuries and resulting complications account for 7% to 8% of deaths in this group. Surveys of general hospitals have shown that pressure sores develop in 3% to 4.5% of patients during their hospital stay. The prevalence of pressure ulceration increases greatly with age, with patients older than 70 years of age accounting for 70% of all those afflicted. In this age group, 70% of all pressure sores develop within two weeks of admission to hospital.

Pathophysiology

The precise mechanism by which pressure sores develop remains to be defined, but there are several factors that appear to be critical. The role of pressure has been most clearly established. The application of pressure to skin and soft tissue leads to increased interstitial pressure that exceeds the pressure in the venous limb and lymphatics, producing vascular and lymphatic occlusion with filtration, autolysis and accumulation of anaerobic metabolic waste. Skin appears to be less sensitive to the effects of vascular occlusion than does muscle. In addition to the vascular and lymphatic effects, there appears to be a direct mechanical effect on skin and muscle as well. The period of time necessary to induce the pressure-associated changes varies among individual patients but apparently averages about two hours. Other important factors are shearing forces, which are produced by an improper position; friction, which occurs with improper handling of a patient; moisture due to perspiration, urine and feces, and spasticity, which may make proper positioning difficult and predispose a patient to shearing and frictional forces.

Clinical Features

More than 90% of pressure sores are located on the lower part of the body, but in an individual patient they are a function of positioning. Trochanteric, ischial and sacral pressure sores are the most common. Figure 1 shows the clinical stages of pressure ulceration. Staging is based primarily on the physical examination, which should include careful palpation and exploration of an ulcer. In higher stage pressure sores, certain radiographic and radionuclide studies, discussed below, may be necessary for accurate staging.

The differential diagnosis of pressure sores is generally not a problem but they may occasionally be confused with perirectal abscesses, cutaneous vasculitis with ulceration, deep mycoses or malignancy.

Complications of pressure ulceration are common and may be life threatening. Infectious complications occur most frequently. Pressure sores are routinely colonized with a wide variety of organisms; Gram-negative enteric organisms and anaerobic organisms appear to be the most important source of wound infection. *Staphylococcus aureus* causes wound infection much

(Cooney TG, Reuler JB: Pressure sores [Topics in Primary Care Medicine]. West J Med 1984 Apr; 140:622-624)

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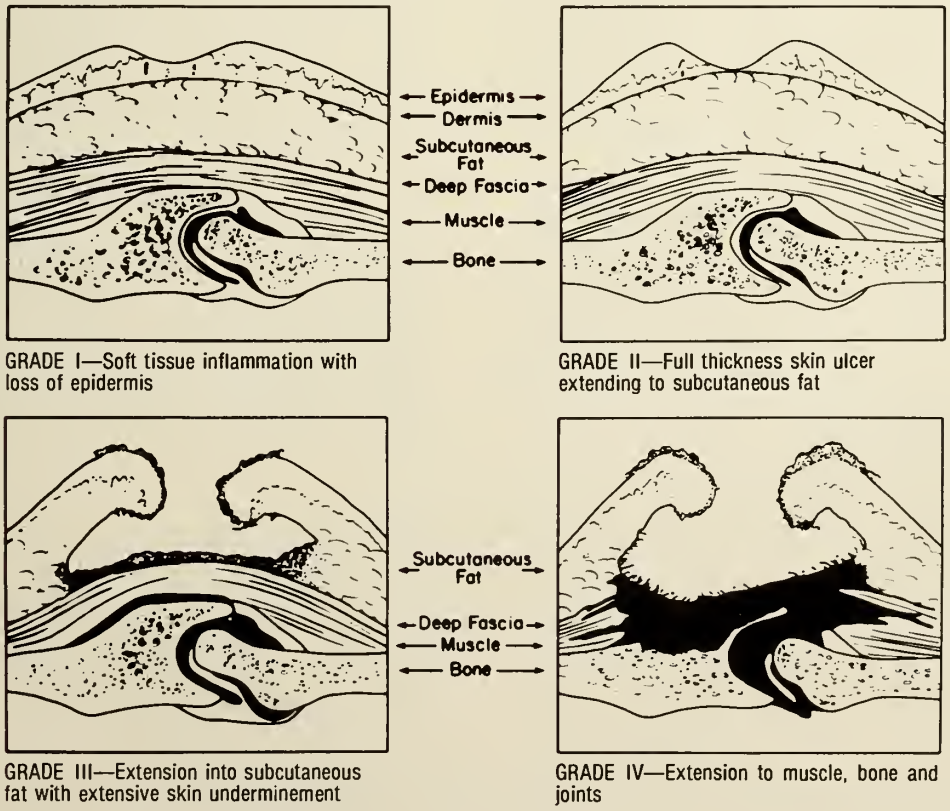
less frequently and usually in sores located distant from the pelvis. Sepsis is a serious and not infrequent complication and carries a high mortality rate in patients older than age 60 years. Anaerobic bacteria, particularly *Bacteroides fragilis,* and enteric Gram-negative organisms are the most common bacteria recovered from blood cultures. There is little information on the effectiveness of various antibiotics in treating infected pressure sores. Cephalosporins have not been shown to penetrate into pressure sores, whereas clindamycin and gentamicin sulfate have achieved therapeutic levels in surgically resected pressure sores.

Osteomyelitis occurs frequently with higher grade pressure sores but can be very difficult to diagnose. Plain radiographs are insensitive (50%) and their findings are relatively nonspecific (82%). Technetium Tc 99m bone scans are very sensitive (100%) but their findings, like radiographs, are nonspecific (50%). Gallium scans are less sensitive (83%) and also have nonspecific results (59%). The role of computerized tomography (CT) remains undefined but it may be helpful in the staging of the larger, high-grade ischial, trochanteric and sacral pressure sores. In a patient who may have osteomyelitis, plain radiography and technetium Tc 99m bone scanning should be done. If either is positive, a bone biopsy and culture should be carried out to confirm histologically the presence of osteomyelitis and to identify the infecting organism. Bone cultures alone are very sensitive (100%) for osteomyelitis but the results are very nonspecific (33%). Wound cultures have a low predictive value in identifying the infecting organisms in osteomyelitis and should not be used to select antibiotic therapy.

Other serious complications include pyarthrosis and extension to deep organs; these may be shown by sinography or CT scanning. Tetanus is a rare complication of pressure ulceration. Given the low prevalence of immunity to tetanus in older patients, however, tetanus immunization should be given to high-risk patients in this age group. Finally, amyloidosis is a well-described but rare complication of chronic pressure ulceration.

Prevention

Without question, prevention is the most important aspect in the management of pressure ulceration. Because of the limitation of resources, it is important to identify patients at high risk for pressure ulcerations so that preventive measures may be intensively but selectively used. A variety of clinical tools exist that are very sensitive and relatively specific in detecting those patients in whom pressure sores are likely to develop (Table 1). Once patients are known to be at risk, specific measures should be used to minimize the critical factors that are implicated in pressure ulceration. Friction and shearing forces should be avoided by proper positioning, relief of spasticity and prevention of soilage. Incontinent patients should be cleaned frequently and every effort made to keep them dry. Natural sheepskin appears to be useful in minimizing the effects of moisture, shearing forces and friction.



GRADE I—Soft tissue inflammation with loss of epidermis

GRADE II—Full thickness skin ulcer extending to subcutaneous fat

GRADE III—Extension into subcutaneous fat with extensive skin underminement

GRADE IV—Extension to muscle, bone and joints

Figure 1.—Clinical stages of pressure sores.

TABLE 1.—*Risk Criteria for Pressure Sores**

Absolute (Score 2)†	*Relative (Score 1)*†
Coma	Age ($\geq$70 years)
Dehydration	Restricted mobility
Paralysis	Incontinence
	Emaciation
	Redness over bony prominence

*From Andersen KE, et al.

†Score >3 indicates a patient is at high risk. Sensitivity 88%, specificity 87%, predictive value (+) 7%, predictive value (—) 99%.

Relief of pressure, however, is the most important factor in preventing pressure ulceration. A variety of pressure relief systems exists for an in-hospital patient, including special mattresses and beds. These systems can be very expensive, many are cumbersome to use and most are subject to mechanical failure. Alternatively, frequent turning (every two hours) and bridging with pillows is inexpensive and very effective. For wheelchair-bound patients, support surfaces and cushions are very important in relieving pressure; these pressure relief systems should be customized to fit the needs of an individual patient. Individualized prescriptions for pressure relief surfaces are available through special rehabilitation units. The importance of relieving pressure in at-risk patients cannot be overemphasized. *Where there is no pressure, there are no sores.*

Management

Once a pressure sore occurs, its management is similar to that of any other wound; the goal is to promote healing. General medical care should focus on nutritional repletion to reverse protein catabolism, to replace fluid and protein losses and to enhance wound healing. The value of supplementation with vitamin C or zinc remains unsubstantiated. Correction of anemia or edema, control of diabetes and improvement in tissue oxygenation and tissue perfusion may all contribute to wound healing.

Most wounds are superficial, and their healing will occur by secondary intention through wound contraction and reepithelialization. Management objectives include relieving pressure, debriding necrotic tissue and suppressing infection. The relief of pressure is best accomplished by frequent turning and bridging through the use of several pillows. Occasionally, patients with many pressure sores will require special support surfaces to facilitate unloading.

A large array of substances have been placed on pressure sores and advocated as being active in accelerating wound healing. Unfortunately, few of these preparations have ever been carefully studied. We suggest the use of simple saline-mesh gauze dressings applied every four hours. This technique has been shown to reduce wound bacterial colony counts and appears to promote healing. Silver sulfadiazine likewise has been shown to reduce wound bacterial colony counts and may be particularly helpful in the initial management of purulent wounds. Povidone-iodine is no more effective than saline; furthermore, in large wounds, systemic absorption of iodide can produce renal and hepatic toxicity. Semipermeable membranes and dextranomer, despite their widespread use and theoretic promise, have not been studied adequately to show that they represent an advance in therapy.

Grades I and II pressure sores are generally successfully managed with local therapy and wound debridement as described above. Higher grade pressure sores, particularly those associated with sepsis, will often require surgical debridement. In the absence of infectious complications such as osteomyelitis, pyarthrosis or sepsis, systemic antibiotics are not indicated. In a patient with serious infectious sequelae, initial antibiotic therapy, pending identification of the causative organisms, should include coverage for anaerobic bacteria, particularly *B fragilis* and Gram-negative enteric organisms. The combination of clindamycin and an antipseudomonal aminoglycoside is a rational choice for empiric therapy.

While the role of more definitive reconstructive surgical therapy in an elderly patient remains to be defined, it is clear that reconstructive surgical techniques play a major role in the management of younger patients with spinal cord injury who have high-grade pressure sores. Excellent dissertations on the surgical management of this problem are available.

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Impact of the Brain Death Ruling in Washington State

DONALD C. TYLER, MD, *and* WILLIAM O. ROBERTSON, MD, *Seattle*

In a 1980 Washington State Supreme Court decision, brain death was recognized as a means of determining death, but the court declined to specify a procedural mechanism to be followed. According to a survey of hospitals in Washington, the decision has had little impact in the state, apparently due to the medical profession's unfamiliarity with it. As a result of the survey, we have identified problems of procedure and interaction with the legal system. A consensus of those contacted was that no formal, hospital-mandated definition of brain death is needed.

(Tyler DC, Robertson WO: Impact of the brain death ruling in Washington state [Critical Issues in Medicine]. West J Med 1984 Apr; 140:625-627)

Late in 1980 the Supreme Court of the state of Washington issued a ruling that recognized brain death as a legal means of determining death in the state. This ruling states that, in addition to traditional criteria, death is defined as "irreversible cessation of all functions of the entire brain, including the brain stem."[1] Of particular note was the court ruling that left the medical profession to determine what findings were diagnostic of brain death. The court said, "We do not address what are acceptable diagnostic tests and medical procedures for determining when brain death has occurred. It is left to the medical profession to define the acceptable practices."[1] While the court's decision could dramatically alter practice in some hospitals, the impact throughout the state of Washington is unclear. To evaluate if brain death has been used to define death in Washington state, and to learn whether or not hospitals have developed formal definitions of death, the following telephone survey was undertaken.

Materials and Methods

One of us (D.C.T.) conducted a telephone survey of the 117 member hospitals of the Washington State Hospital Association. A knowledgeable person—in most cases the medical director of the intensive care unit, the chairperson of the critical care committee, the head nurse or intensive care supervisor—was interviewed, and in a few instances a member of the hospital administration was interviewed. If a respondent was unfamiliar with current practice another person was contacted. No person was interviewed if he or she admitted to being unfamiliar with current practice in the hospital.

The following six questions were developed after we evaluated the responses from the first five hospitals:

1. Do your physicians distinguish brain death cases from cases in which life support is discontinued because of a hopeless prognosis per se?
2. Have any formal criteria been developed by the hospital to be used to determine brain death?
3. Are similar criteria followed in cases that involve potential legal problems (such as child abuse, attempted homicide or organ transplants)?
4. Is the decision that brain death has occurred reviewed by a review committee, by the medical director or in any other fashion?
5. Has this topic caused significant problems at your hospital? If so, what sorts of problems?
6. Are you aware that the Washington State Supreme Court has issued an opinion as to the declaration of brain death? If so, are you aware of the details?

The questions were asked in an open-ended fashion with clarification solicited when necessary.

Results

Cooperation among the respondents was excellent. Interest appeared to be high. Of the 117 hospitals, 43

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had no intensive care unit; they were excluded from the survey. The other 74 hospitals each provided information.

In 55 cases the chair of the critical care committee or the medical director was interviewed, in 15 instances the head nurse or supervisor was interviewed and in four instances, an administrator. The responses to the six questions are tabulated below.

1. In 57 hospitals (77%) it is common practice to differentiate cases of brain death from those in which the patient is hopelessly comatose but still technically alive. In 17 hospitals (23%) no apparent distinction is made.

2. In all, 67 hospitals (91%) have not adopted formal criteria for determination of brain death; 7 hospitals (9%) have formal criteria that are adopted as hospital policy. Generally, these criteria follow the Harvard Criteria,[2] the National Institutes of Health Criteria[3] or the British Criteria.[4]

3. Of the 74 hospitals, 22 (30%) had not had cases involving "extraordinary" legal situations and, therefore, had not confronted the issue of what to do in such situations. Seventeen other respondents reported that for such legal cases, they would determine brain death according to the usual definitions and discontinue support in accordance with their usual practices. In contrast, 30 hospitals (40%) reported that when an extraordinary case arose, a different approach to documentation of brain death had been or would be followed. Specifically, in one hospital the chief of staff would be personally involved, in two hospitals the county's medical examiner or coroner would be involved and, in the rest of the hospitals, additional consultation about, or extra documentation of, the determination of brain death would be obtained.

4. In 63 hospitals (85%) no review is required of a brain death determination. In these hospitals, apparently a single physician can make that determination and discontinue support systems. In 26 of those hospitals, however, a consultation is usual and customary in such a situation. In contrast, for 11 hospitals (15%) there is a formal review mechanism, with four requiring a neurologic consultation, one involving the executive committee of the hospital, two involving the medical director of the intensive care unit and four involving a second physician's participation.

5. In all, 56 hospitals (76%) reported no problems involving brain death determinations or discontinuation of life support in their institutions, whereas 18 (24%) reported that problems had occurred. Five of these hospitals had been involved in litigation concerning discontinuation of life support. Admittedly, four of those cases were not situations in which brain death was at issue; rather, the issue was one of discontinuing life support in patients who did not meet predetermined brain death criteria. The fifth case was the one from which the state's supreme court brain death decision arose. During our survey a major problem perceived among respondents emerged—that is, there is a general perception among nursing staff that physicians are not aggressive enough in discontinuing life support, that they do not confront the issue and that they tend to maintain patients on life support exceptionally long. Moreover, in two hospitals nurses have asked for reviews of decisions with which they did not agree. In two other hospitals questions arose of how to proceed once a brain death has been determined—that is, how to deal with family and staff and when and in what manner life support should be discontinued.

6. Of the 74 respondents, 42 (57%) reported that they were familiar with the decision of the Washington State Supreme Court, whereas 32 (43%) were not familiar with that decision. Of those familiar with the decision, 29 claimed to be familiar with the details. Thus, 45 respondents were either unacquainted with the decision or not conversant with the details of the decision.

Discussion

Clearly the decision of the Washington State Supreme Court has not had widespread impact some three years after it was rendered. Part of the reason appears to be ignorance of the decision, occurring in over half the hospitals surveyed. Although the mass media and professional newsletters carried information about the decision, no formal communication had been directed toward physicians in the state of Washington concerning a major change in the legal definition of death. It is therefore not surprising that a large proportion of physicians are unfamiliar with that decision.

Following the Washington State Supreme Court decision, some observers questioned whether formal brain death criteria ought to be adopted. Interestingly, two years later, few of the intensive care units in the state had adopted a formal mechanism to determine brain death; most were leaving the matter of definition to the individual physicians involved. Because many hospitals do not have electroencephalographic equipment or other advanced forms of technology available, this approach may be appropriate. Obviously different means may have to be used to determine brain death in different locations. With advancing technology, newer techniques may become available and, if formal criteria were to be adopted, these criteria would have to be updated to keep pace with advancing technology. Such an approach to defining brain death is consistent with the position recently published in the *Journal of the American Medical Association*.[5]

That 30 hospitals used or would use a different approach to the definition of brain death and documentation thereof in cases that involve extraordinary legal problems probably reflects two concerns. One is the unfamiliarity with the brain death decision and, therefore, hesitancy to use brain death as a legal means of determining death in appropriate patients. The other reflects an understandable paranoia of physicians about medicolegal matters and their feeling that extra docu-

mentation or a preponderance of medical opinion needs to be obtained for any case likely to involve the courts.

A large proportion of hospitals denied having a required review of brain death decision. Because there is no review when death is determined by cessation of heart beat and respiratory function, this lack of a review process may simply reflect the usual approach to the determination of death or it may indicate that no local controversy has arisen.

A large majority of respondents reported no problems with brain death decisions, but several legal issues have arisen in this state with regard to discontinuing life support in a patient who does not meet brain death criteria. Clearly, the issue of discontinuing life support in a patient who does not meet the criteria calls for clarification, and the recent Colyer[6] decision of the Washington State Supreme Court appears to address some of these issues, though other cases are still pending in the courts.

Several hospitals have questioned how to proceed once brain death is determined. The general approach in this state appears to be to pronounce a patient dead at the time of the determination of brain death and then to discuss the options with the family. At this point, most families express a desire to see the patient one last time; generally they are permitted to do so, during which time life support is continued. Following the visit life support is discontinued. The time of death is recorded as the time when brain death had been determined, as opposed to the time of cessation of heart beat.

In summary, our data indicate that the brain death decision of the Washington State Supreme Court has had surprisingly little impact throughout the state, largely because of apparent physician ignorance of this means of determining death. Clearly, there needs to be a more effective process of informing physicians of major changes in such legal aspects of medicine. A consensus of the physicians surveyed was that no formal mechanism needs to be set up to determine brain death in their hospitals and that no formal review of the process should be required. At the same time there is a continuing need to clarify some of the legal issues involved in discontinuing life support in patients who do not meet brain death criteria, but who apparently have no possible hope of recovering.

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Determination of Brain Death

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With the careful application of the principles outlined herein, brain death can be determined with certainty. There have been no documented reports of survivors when these guidelines have been followed. The triad of a known mechanism of brain injury, absence of contributing metabolic or toxic central nervous system depression and absence of demonstrable brain function is sufficient to determine brain death clinically and, in most states, legally. The use of apneic oxygenation protects cadaver organs for transplantation during the period needed to prove that a patient cannot breathe.

Very little can ameliorate the tragedy of sudden and unexpected fatal cerebral injury. Nonetheless, the concept of brain death is well established, and there is no longer a medical or an ethical reason to prolong unnecessary support of these patients.

(Pitts LH: Determination of brain death [Critical Issues in Medicine]. West J Med 1984 Apr; 140:628-631)

The recent report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research devoted considerable attention to the questions of defining death generally[1] and brain death specifically.[2] The concept of brain death, defined as the irreversible loss of all function of the cerebrum, the cerebellum, the midbrain, the pons and the medulla, is no longer very controversial among clinicians in the United States. However, during a recent nationally televised debate in Great Britain, claims were made that some patients had survived termination of life-support systems despite a diagnosis of brain death.[3] A review of the cases in question showed that no patient who survived termination of life support had been declared brain dead. Additionally, a review of published instances of brain death[3] and a review of data banks that have extensive information on central nervous system (CNS) disease[1,3] did *not* identify *a single instance* of patient survival, for even brief periods, after brain death had been determined using the proper criteria. Conversely, none of more than 1,000 patients with severe head injuries who survived ever were suspected of being brain dead, even during their worst clinical states.[3]

Medical professionals must be able to accurately determine if a patient is brain dead so that life-support systems can be withdrawn in a timely manner to prevent unjustified use of precious critical care facilities and to provide donor organs for transplantation. The success of renal transplantation and continuing attempts to transplant other vital organs require that appropriate donor candidates be identified and that their neurologic status be defined carefully to assure that they are indeed "beating heart cadavers" before organs are harvested. Transplant surgeons are extremely cautious and insist that candidates cannot be considered for organ donation until after they are declared to be brain dead. Because incorrect or questionable criteria have sometimes been used to evaluate brain death, occasionally incorrect diagnoses of brain death have been made. Rarely, organs have been harvested from patients who were not brain dead at the time of organ removal; patients have survived for short periods after organs were removed. Such errors invariably can and must be avoided by applying proper criteria for determining brain death.

Laws regarding brain death vary from state to state. California has an excellent law that requires only that brain death be certified by two physicians and does not require undue and unnecessary technologic verification of brain death. (Pertinent sections of the statute are reprinted in Figure 1). I believe that this law is

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CT = computed tomography
EEG = electroencephalography

appropriate, expedient and correct and rightly places responsibility on physicians who are called on to determine if a patient is brain dead. Although a diagnosis of brain death does not have to be made by neurologists or neurosurgeons only, it is imperative that other physicians who may be in a position to make this diagnosis are confident of their knowledge of the criteria with which brain death can be determined and of their ability to apply them properly. I hope that the following discussion of these criteria will make this process easier for all clinicians.

Criteria for Determining Brain Death

Criteria to determine brain death described below are used at the San Francisco General Hospital Medical Center, a regional trauma center that treats a large number of patients who ultimately die of head injury. It should be emphasized that most patients who die after head injury typically are not brain dead until the time of terminal cardiopulmonary failure and arrest. The clinical course of these patients is characterized by coma with spontaneous ventilation and other brain-stem function for some days or weeks after severe head injury; patients usually die of infection or ventilatory complications of protracted unconsciousness. Thus, criteria for the diagnosis of brain death can be applied properly to only a relatively few of these patients.[1]

The diagnosis of brain death requires that the cause of CNS dysfunction be known, that no toxic or metabolic factors that could depress neurologic function be present and that there be no demonstrable brain function (Table 1). While a number of electrophysiologic, radiologic or nuclear medicine studies may provide additional proof of brain death, generally these studies need not be done in typical patients. However, it is necessary occasionally to do one or more of these tests in patients whose clinical course is complicated, or who have a myriad of apparently unrelated clinical signs or results of laboratory tests (or both) that can make a diagnosis extremely difficult. An example of such a patient might be one with prolonged unconsciousness, no evidence of brain function, negative toxicologic studies and a nondiagnostic computed tomographic (CT) scan for whom no definitive cause for apparent brain death has been established.

The Cause of Brain Damage Must Be Known

A diagnosis must be established. This can be done clinically in instances of severe open head injury, gunshot wounds of the brain, prolonged cardiac arrest, drowning with recorded long periods under water or other *very obvious* causes of brain damage. Without such convincing clinical evidence, diagnostic studies should be done to determine the nature and extent of the brain lesion; a CT scan provides the most readily available and definitive documentation of structural damage such as unilateral or bilateral cerebral infarction, massive intracerebral hemorrhage or other cerebral mass lesions that would account for failure of cerebral and brain-stem function. In a few patients with basilar artery occlusion that leads to brain death, early CT scans may show no abnormalities and cerebral angiography will be necessary to delineate the pathologic features. In the absence of clear clinical or radiographic evidence of overwhelming brain damage, a clinician must be extremely cautious in diagnosing brain death; patients should be supported for one or more days, during which time appropriate additional diagnostic information can be obtained.

Metabolic and Toxic CNS Depression Must Be Excluded

Many systemic abnormalities will depress central nervous system function and should be corrected as completely as possible before the diagnosis of brain

Article I

§ 7180. **Determination of death; irreversible cessation of circulatory and respiratory or brain functions**

(a) An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards . . . .

Article II

§ 7181. **Independent confirmation of brain function cessation**

When an individual is pronounced dead by determining that the individual has sustained an irreversible cessation of all functions of the entire brain, including the brain stem, there shall be independent confirmation by another physician . . . .

§ 7182. **Independent confirmation when part of donor used for direct transplantation**

When a part of the donor is used for direct transplantation . . . and the death of the donor is determined by determining that the individual has suffered an irreversible cessation of all functions of the entire brain, including the brain stem, there shall be an independent confirmation of the death by another physician. Neither the physician making the determination of death . . . nor the physician making the independent confirmation shall participate in the procedures for removing or transplanting a part.

Figure 1.—Pertinent sections of the Uniform Determination of Death Act of the State of California (Chapter 3.7 of the California Health and Safety Code).

TABLE 1.—*Criteria for Determining Brain Death*

Known mechanism of injury
Absence of toxic or metabolic central nervous system depression
Absence of brain function

death is considered. Systemic hypotension or intracranial hypertension, singly or in combination, can lower cerebral perfusion and depress CNS function. Hypothermia lowers cerebral metabolism and can depress brain function, though coma as a result of hypothermia alone does not occur if core body temperatures are above 32°C (90°F). Temperatures between 27°C (80°F) and 32°C can cause coma and temperatures below 27°C virtually always cause coma.[4] Severe hyponatremia may increase brain water content profoundly and cause severe cerebral edema, thereby depressing brain function. Hyponatremia also may cause focal or generalized seizures, the presence of which excludes a diagnosis of brain death. Poor ventilatory function with hypoxemia or hypercarbia can depress cerebral function and should be corrected. While it is unlikely that any of these metabolic disorders can cause cessation of cerebral function, any might depress minimal brain function to the point that an incorrect diagnosis of brain death could be made.

Systemic toxins alone *can* produce apparent brain death in patients who can recover with absolutely normal neurologic function if they are supported during the period of intoxication. Thus, it is *imperative to exclude an intoxicated state,* either by reliable history (for example, the patient being normal immediately before trauma or having a dramatic and abrupt neurologic ictus consistent with intracranial hemorrhage) or by appropriate toxicologic screening before the diagnosis of brain death is made. Barbiturate overdose can abolish all clinically detectable brain function, though brain-stem evoked potentials often are present even in the absence of other demonstrable brain function. Other hypnotic or sedative agents can greatly depress CNS function to the point that brain-stem reflexes are lost. Ethanol intoxication also can depress CNS function, though it is exceedingly unlikely that the effects of ethanol intoxication alone can mimic brain death.

An appropriate toxicologic screen for CNS depressants should be carried out on blood and urine specimens. Even in patients known to have structural brain lesions, toxins must be excluded before the diagnosis of brain death can be made reliably.

There Must Be No Demonstrable Brain Function

Neurologic testing must show that there is no *brain-generated* response to any neural stimulus (Table 2). Some brain dead patients retain spinal cord reflexes. Thus, minor flexion of upper or lower extremities with local extremity pain need not preclude the diagnosis of brain death. With medullary failure, however, spinal shock generally intervenes and deep tendon reflexes and segmental withdrawal reflexes are absent.

A patient would have no response to supraorbital pain stimulus because sensory input to the brain is via the trigeminal nerve into the brain-stem trigeminal nuclei. Pupils will be mid-dilated (5 to 6 mm in size), with loss of neuronal response of both hypothalamic sympathetic cells and of parasympathetic cells in the Edinger-Westphal nucleus located in the rostral midbrain. Pupillary response to light is absent because death of the upper midbrain causes loss of optic nerve input and parasympathetic nerve output from that region. No eye movement can be elicited either by the doll's eyes maneuver or by cold water caloric testing because pontine vestibular nuclei are without function, as are the pathways for coordination of eye movement in the medial longitudinal fasciculus that extends from the third nerve nucleus in the upper midbrain down to upper cervical spinal cord segments, where joint-position sensation of the cervical spine enters the medial longitudinal fasciculus for coordinating eye movement. Corneal reflexes in both eyes are absent with loss of trigeminal sensation input and facial nerve output to the orbicularis oculi. There is no gag response to firm tongue blade pressure against the oropharyngeal wall. There is no cough reflex with tracheal suctioning via an endotracheal tube. Finally, a patient must be apneic in the presence of an *adequate* carbon dioxide stimulus.

TABLE 2.—*Absence of Brain Function*

No pupillary response to light
No corneal reflex
No eye movement with doll's eyes maneuver or caloric testing
No response to supraorbital pain
No gag reflex
No cough reflex
Apnea

Because hypoxemia with prolonged apnea can cause cardiac arrest and complicate possible organ removal for transplantation, proper apnea testing[5] is necessary and is summarized here. A patient should be ventilated for five minutes with 100% oxygen at normal tidal volumes so that arterial levels of oxygen are greatly elevated and levels of arterial carbon dioxide are normal (about 40 mm of mercury) at the time that ventilation is discontinued. The ventilator then is replaced by a T-piece delivering pure oxygen to replace oxygen removed from the alveoli by circulating blood. The patient is observed carefully for evidence of respiratory efforts; if none occur within 10 to 15 minutes, during which time the partial arterial carbon dioxide pressure usually will increase 30 to 45 mm of mercury, then apnea will have persisted despite an intense respiratory stimulus. This method of apneic oxygenation ensures that a patient has no response to apnea, a sine qua non of brain death, but will maintain an adequate partial arterial oxygen pressure for 15 minutes or more (in the absence of lung diffusion abnormalities) and protect organs that are potentially available for transplantation.

In a few instances, patients being ventilated mechanically are given muscle relaxants during treatment and the ability of a patient to respond to neurologic testing might be questioned. Most paralyzing agents used in this setting are metabolized within a few hours of administration. Even in unusual circumstances such as the use of aminoglycoside antibiotics in patients with renal failure or in rare instances of prolonged paralysis

TABLE 3.—*Supporting Examinations to Confirm Brain Death*

Electroencephalography	Radionuclide brain scan
Brain-stem evoked responses	Intracranial pressure monitoring
Cerebral angiography	

from the use of a single injection of succinylcholine chloride, paralysis can be assessed using a nerve stimulator and observing an appropriate muscle twitch response. If possible paralysis is a concern, the issue should be resolved through consultation with an anesthesiologist.

There are no special precautions for pronouncing brain death in infants and children. Even very young infants have well-developed brain-stem reflexes, and absence of these reflexes is the cornerstone of a diagnosis of brain death. The usual precautions must be followed, including an accurate diagnosis for destructive brain lesions and the absence of CNS depression. Because it is often difficult for families to accept the death of a child, to allow the family time to adjust to the tragedy, some delay—perhaps up to a day—might be justified before ventilation is discontinued.

Additional Examinations That Can Be Made to Verify Brain Death

Results of several electrophysiologic, radiologic and other tests can be used when necessary to confirm a clinical diagnosis of brain death (Table 3). Since publication in 1968 of the Harvard Brain Death Criteria,[6] electroencephalography (EEG) has been used frequently to confirm brain death. It has been suggested that two EEGs that record electrocerebral silence[7]—a "flat" EEG—must be obtained 6 to 24 hours apart before brain death can be diagnosed with certainty. The use of EEG is not required in California, though it is sometimes reassuring to clinicians, especially in difficult or uncertain cases, to prove the absence of electrocerebral function. If there is a known cause of brain destruction, absence of contributing metabolic or toxic CNS depression and absence of demonstrable brain function, we do not do an EEG. In patients for whom the diagnosis is uncertain, or if one of our clinicians desires support of the clinical diagnosis, an EEG may be done. However, a single flat EEG is enough to confirm brain death.

Cessation of cerebral circulation also invariably produces brain death. The absence of cerebral blood flow can be shown by arteriography,[8] during which a carotid injection of iodinated contrast material will fill the cervical carotid artery but will not enter the intracranial space, producing what is referred to as a "carotid stop." If brain death is strongly suggested in a patient known to have barbiturate intoxication, absence of intracranial flow will allow a diagnosis of brain death regardless of the *degree* of intoxication. Radioisotopes injected intravenously will not enter the cranial space, and a brain scan will show no intracranial flow.[9] Care must be taken with radioisotope studies to ensure that extracranial circulation is not misinterpreted as intracranial flow.

Both auditory and somatosensory evoked potentials of the brain stem can be used to prove brain death.[10] They may be particularly valuable in *excluding* brain death in cases of barbiturate coma, which can produce absence of demonstrable brain function and a flat EEG, by showing that there are brain-stem evoked responses. In brain dead patients, all components of the brain-stem auditory evoked response will be absent except for wave I, which arises from the cochlea in the ear and may be present despite brain death.

Monitoring intracranial pressure may show the presence of intracranial hypertension that equals or exceeds arterial pressure. This lack of cerebral perfusion will produce complete cerebral ischemia and death within five to ten minutes.

None of these procedures is required for proof of brain death in many states, including California, and in my opinion should be reserved for those patients for whom there is considerable uncertainty about the clinical picture or some reason to doubt the reliability of the clinical examination.

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Special Article

Cancer, Passive Smoking and Nonemployed and Employed Wives

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Passive smoking (inhalation by nonsmokers of tobacco smoke produced by smokers) as a cause of cancer is presently a topic of intense debate. Short-term passive smoking has long been associated with irritation of the eyes and allergic reactions,[1] although the overall effect was believed to be inconsequential. Passive smoking by children exposed in households of smoking parents has been shown in most studies to cause a twofold increase in the incidence of pulmonary diseases.[1] Despite studies reporting high concentrations of various carcinogens in both main- and side-stream tobacco smoke,[2] the potential effect of passive smoking was considered negligible.

Only recently have the effects of long-term passive smoking (two or more decades of exposure) been studied. The first report of findings was published in 1978 by Miller.[3] This information was reported a year later at the Fourth World Conference on Smoking and Health in Stockholm.[4] Additional findings were reported by White and Froeb,[5] Hirayama,[6] Trichopoulos and co-workers[7] and Garfinkel.[8] Four of the five reports showed significant support for the hypothesis that passive smoking is associated with increased health risks, and one showed positive but nonsignificant results.

The present study was devised to investigate the health effects of long-term passive smoking on nonsmoking women by comparing a group of wives with little or no exposure with a group of wives with long-term exposure. The measurement of the effect of this exposure is by noting deaths from cancer. Because nonsmoking wives whose husbands also do not smoke may, nevertheless, be exposed to passive smoking in an out-of-the-home workplace, there is a problem of properly classifying passive smoking exposure. To investigate this potential out-of-the-home confounding factor, two comparisons of passive smoking were made—one including employed wives and one excluding employed wives.

Subjects and Methods

The Northwestern Pennsylvania Study of Smoking and Health (NPSSH) began in 1973 to gather data on the smoking habits of deceased persons in Erie County (Pennsylvania) by interviewing the deceased's next of kin. Death notices for the years 1972 through 1976 were obtained from the local newspaper, which lists the names of nearly all Erie County residents who have died and information on surviving relatives.

The 1970 Erie County population was 263,654, which includes Erie, the third largest city in Pennsylvania. The population of Erie County is primarily a middle-income group (the average family income for 1970 was listed as $9,380[9]) with a low migration rate (7%) for the 1950-1970 time period as reported by the Pennsylvania Department of Commerce.

Telephone numbers of one to three surviving relatives were obtained for each death notice whenever possible. Telephone numbers could not be located for about 15% of the cases due to factors such as no surviving relatives in Erie County, unlisted telephone numbers or the transient status of the deceased. Deaths due to accidents, suicides, congenital anomalies and in persons younger than 30 years of age were not included.

Construction of a questionnaire for the interviews was completed with the assistance of the local branches of the American Cancer Society, the American Heart Association and the American Lung Association and by members of the Pennsylvania Department of Health. A more detailed description of this questionnaire has been reported elsewhere.[10]

Interviewers explained the purpose of the study to the identified surviving relatives and solicited their cooperation. Information was collected on each deceased's cause of death, age, occupation (including information on whether or not the wife worked outside the home) and smoking history, as well as whether or not the spouse and parents smoked. The interviews were conducted by the director of the study and qualified interviewers trained by him. The questionnaire was revised in 1975 to obtain more complete information on a spouse's smoking habits such as type and quantity of tobacco used, the age of the spouse at the time of death or the current age if living, and the year or

(Miller GH: Cancer, passive smoking and nonemployed and employed wives. West J Med 1984 Apr; 140:632-635)

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TABLE 1.—*Mean Age of Death By Cause of Death for Nonsmoking Women (Erie County, Pennsylvania), 1975-1976*

Group	Cause of Death Cancer	Number	Cause of Death Other Than Cancer	Number
All Women				
Smoking husband	67.58	89	75.33	270
Nonsmoking husband	70.58	34	82.95	144
Nonemployed Women*				
Smoking husband	68.56	66	76.62	238
Nonsmoking husband	71.72	18	84.12	126

*Does not work outside the home.

decade of death if deceased. These additional items permitted a more detailed analysis of the effects of passive smoking. Among the relatives contacted, 95% provided information for the study.

For the purposes of this study, a nonsmoker was considered to be one who had smoked fewer than 20 packs of cigarettes during his or her lifetime. An employed wife was identified by a surviving relative as a full-time employee in an occupation other than housework.

The most complete data were from the 1975-1976 interviews and therefore will be the only data considered in this report. A total of 4,130 deceased were located in the death notices for Erie County in the first 20 months of 1975 and 1976. Forms were completed for 3,288 of the deceased by the research assistants. A total of 842 deceased listed in the death notices were not included in the study for the following reasons:

No survivors in Erie County	685
Younger than 30 years of age	130
Accidents (listed in death notices)	27
TOTAL	842

The interviewers completed 1,838 interviews from the 3,288 completed forms. Information was not obtained for 1,450 deceased for the following reasons:

Lack of funds to complete interviews	1,091
Inability to locate relatives	292
Age younger than 30; accidents; refusals	67
TOTAL	1,450

A final total of 537 nonsmoking women was obtained from the 1,838 interviews after deleting the following categories:

Smoking men	825
Nonsmoking men	194
Smoking women	204
Single women	24
Insufficient information on passive smoking	54
TOTAL	1,301

To simplify problems of classification, husbands were considered nonsmokers if they satisfied the definition of not smoking more than 20 packs of cigarettes during their lifetime. All other persons classified as light smokers, moderate smokers, heavy smokers, former smokers and smoking husbands who died during any stages of the marriage were considered smokers. Although information was available for the different types of smoking classifications, a more detailed analysis would have provided subclassifications too small to make valid comparisons.

The nonsmoking wives were analyzed in the following ways:

- All wives
  HNS—husbands did not smoke (no exposure)
  HSM—husbands did smoke (long-term exposure)
- Excluding employed wives
  XHNS—husbands did not smoke (wives did not work outside home)
  XHSM—husbands did smoke (wives did not work outside home)

The data were analyzed in a manner appropriate for a retrospective case-control study.[11,12] The wives of smoking husbands and those of nonsmoking husbands were separated into the following categories by cause

TABLE 2.—*Causes of Death in All Women in Relation to Husbands' Smoking History*

Age Group Years	Husbands' Smoking Group	Deaths Due to Cancer Number	Deaths From Other Causes Number	Deaths Due to Cancer Percent	Odds Ratio	χ^2
80 and older	Smoker	14	150	0.09	1.28	0.27
	Nonsmoker	8	110	0.07		
70 to 79	Smoker	27	87	0.24	0.62	1.24
	Nonsmoker	11	22	0.33		
60 to 69	Smoker	22	20	0.52	0.40	1.99
	Nonsmoker	11	4	0.73		
59 and younger	Smoker	26	13	0.61	4.00	4.21*
	Nonsmoker	4	8	0.33		
TOTAL GROUP	Smoker	89	270	0.34	1.40	2.18
	Nonsmoker	34	144	0.19		
MEDIAN AGE	Smoker	68.0	81.0			
	Nonsmoker	71.8	83.4			

*This value is significant at the .05 level of significance.

of death: those who died of any form of cancer, and those who died of any other cause.

The classification of the cause of death was based on the primary designation of death indicated by a surviving relative. Although a relative's classification may not be as accurate as a physician's in identifying the actual site of the original cancer, both are aware of whether or not the primary cause of death was due to cancer. There were only five deaths due to lung cancer reported in the entire group. The number was too small to provide stable results using standard statistical techniques; therefore, all causes of cancer were combined. This method thus avoids the problem of establishing the primary site.

Results

The mean age at death for the four groups listed above is given in Table 1. The odds ratio, percentage of deaths due to cancer and χ^2 analysis by age groups (aged 80 years and older, 70 to 79, 60 to 69, aged 59 years and younger and total for all age groups) are reported for the HNS and HSM groups in Table 2 and for the XHNS and XHSM groups in Table 3. Table 4 has similar data for women working outside the home; however, χ^2 analysis was not completed due to the small sample size.

Table 2 (all wives) shows a highly positive but not statistically significant association between long-term passive smoking and cancer as a cause of death for the entire group. The odds ratio is 1.40 and the χ^2 value is 2.18 (P .15) for all wives.

When women working outside the home are omitted (Table 3), the odds ratio increases to 1.94, which is statistically significant ($P<.02$). Thus, long-term passive smoking appears to nearly double the risk of death

TABLE 3.—*Cause of Death in Nonemployed Wives* in Relation to Husbands' Smoking History*

Age Group Years	*Husbands' Smoking Group*	*Deaths Due to Cancer Number*	*Deaths From Other Causes Number*	*Deaths Due to Cancer Percent*	*Odds Ratio*	χ^2
80 and older	Smoker	11	145	7.1	1.93	1.35
	Nonsmoker	4	102	3.8		
70 to 79	Smoker	22	72	23.4	0.61	0.99
	Nonsmoker	8	16	33.3		
60 to 69	Smoker	16	11	59.2	1.94	0.61
	Nonsmoker	3	4	42.8		
59 and younger	Smoker	17	10	63.0	2.27	0.93
	Nonsmoker	3	4	42.8		
Total Group ..	Smoker	66	238	21.7	1.94	5.44†
	Nonsmoker	18	126	12.5		
Median Age ...	Smoker	69.5	81.9			
	Nonsmoker	75.0	83.9			

*Does not work outside the home.
†Significant at $P=.05$.

TABLE 4.—*Cause of Death in Wives Who Worked Outside the Home in Relation to Husbands' Smoking History*

Age Group Years	*Husbands' Smoking Group*	*Deaths Due to Cancer Number*	*Deaths From Other Causes Number*	*Deaths Due to Cancer Percent*	*Odds Ratio*
80 and older	Smoker	3	5	37.5	1.2
	Nonsmoker	4	8	33.3	
70 to 79	Smoker	5	15	20.0	0.66
	Nonsmoker	3	6	33.3	
60 to 69	Smoker	6	9	40.0	...
	Nonsmoker	8	0	100.0	
59 and younger	Smoker	9	3	75.0	12.0
	Nonsmoker	1	4	20.0	
Total Group ..	Smoker	23	32	41.9	0.80
	Nonsmoker	16	18	47.1	
Median Age ...	Smoker	65	73.3		
	Nonsmoker	69	75.0		

from cancer for nonsmoking women with smoking husbands compared with nonsmoking women with nonsmoking husbands.

The proportion of cancer deaths in this Erie County group (excluding confounding factors such as persons younger than 30 years and traumatic deaths) was 22.9%, which is comparable to the 22.68% for the national average reported by the American Cancer Society.[13]

When wives who work outside the home are included, the odds ratio for the aged 59 years and younger group is high and the result is statistically significant (P .05). When this category of wives is excluded, the odds ratios for all age groups other than the 70-to-79-years age groups are 1.93 or higher.

Discussion

The results of the study provide support for the hypothesis that long-term passive smoking leads to excess cancer deaths in exposed nonsmokers.

This conclusion is based on the almost twofold increase in the mortality due to cancer among nonemployed wives who had long-term exposure to passive smoking compared with nonemployed wives with little or no exposure.

The suspicion that wives who work outside the home are exposed to a different environment is supported by the somewhat different results in Tables 2 and 3. For employed wives, the fact that the husbands smoked or did not smoke seems to be unimportant (Table 4). Instead of the non-smoke-contaminated air of a household in which both spouses are nonsmokers, a nonsmoking wife may find herself breathing smoke and other hazards in a workplace. Clerks, secretaries, teachers, nurses and factory workers are among those who may be exposed to carcinogens in work areas or lounges.

This confounding factor of working outside the home with respect to passive smoking and other potential pollutants can explain the differences in the results reported in the studies of Hirayama, Trichopoulos and associates, and the study of Garfinkel. The Hirayama study took place in Japan and the Trichopoulos study in Greece. In both of these countries there are fewer wives working outside the home. Nonemployed wives in these countries are likely to have little contact with tobacco smoke outside the home. The large American Cancer Society sample that was originally reported by Hammond[14] was the data base for the Garfinkel study. This sample was from a relatively more affluent social class likely to contain many women who worked or volunteered outside the home.

Because the Hirayama and Trichopoulos studies had a negligible number of employed wives in their sample, comparisons were made between relatively "pure," nonexposed groups and long-term exposed groups for an analysis of passive smoking. The Garfinkel report, on the other hand, included partially exposed nonsmoking women in the so-called nonexposed groups, thus reducing any potential difference between his two groups. This difference in the composition among the groups being compared is a likely explanation of why the Hirayama and Trichopoulos studies and the present study (with employed wives excluded) show a twofold to threefold increase in mortality from cancer associated with long-term passive smoking, whereas the Garfinkel study shows a smaller but still positive relative risk.

The odds ratio in Table 2 in which wives working outside the home are included is 1.40. The Garfinkel study reports a value of 1.37 for the mortality ratio of wives exposed to tobacco smoke from husbands who smoked less than a pack a day. Although one must be cautious in comparing the odds ratio and the mortality ratio, the similarity cannot be disregarded.

The significant difference reported in Table 2 for the group aged 59 years and younger derives from a fourfold increase in relative risk related to passive smoking. While this might appear to be high, an analysis of the same age group for husbands engaged in agriculture in the detailed Hirayama data[15] gave a similar result—that is, the mortality ratio of wives whose husbands smoked is 3.63 times greater than that of the nonexposed wives. This value is similar to the Erie County result. Whereas the data from this study show borderline significance for the effect of passive smoking and cancer, an analysis of Tables 2 and 3 shows high odds ratios in the lower age categories and small cell values. Therefore, the data base should be increased to determine whether or not these trends continue with a larger population sample.

Additional properly designed studies are necessary on the hazards of passive smoking. Nevertheless, the data now available indicate that the best policy for a nonsmoking person should be to avoid exposure to tobacco smoke whenever possible.

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Commentary

What to Do Because Evidence Links Involuntary (Passive) Smoking With Lung Cancer

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Most discussions of the quality and implications of a specific piece of biomedical research take place in journals such as this, professional committee meetings and in dimmed hotel rooms where the participants strain to see slides packed with data in too-small print. Not so when discussing the question of whether or not breathing secondhand tobacco smoke increases a nonsmoker's risk of lung cancer developing. The Tobacco Institute has spent millions of dollars running advertisements in major newspapers and magazines such as *Time, Newsweek, US News and World Report, People, Sports Illustrated* and *TV Guide* attacking the first study, published by Hirayama[1] in 1981, that showed that nonsmoking wives of smoking husbands are at a higher risk for lung cancer than nonsmoking wives of nonsmoking husbands. Since then, three more studies have appeared on the question of involuntary smoking and lung cancer, two showing a statistically significant increase in risk[2,3] and one showing an increase too small to reach statistical significance.[4] This collection of data from widely different parts of the world (Japan, Greece and the United States) is leading to a consensus in the biomedical community that involuntary smoking is a significant health hazard.[5,6]

There are more than 30,000 studies on the effects of smoking on a smoker, but only about 300 studies of the health effects of breathing tobacco smoke on a nonsmoker. These relatively new studies confirm what scientific common sense suggests: Since the side-stream smoke from the burning end of a cigarette contains the same toxins as the primary smoke a smoker inhales, these toxins affect nonsmokers who breathe them. Yet it is surprising that these relatively few reports have generated such concern in the tobacco industry. To understand why, one need only consult a confidential poll conducted for the Tobacco Institute in 1978 that was subpoenaed and subsequently made public by the Federal Trade Commission.[7] In the report of the findings, it was concluded that

> The original Surgeon General's report, followed by the first "hazard" warning on cigarette packages, the subsequent "danger" warning on packages, the removal of cigarette advertising from television and the inclusion of the danger warning in cigarette advertising were all "blows" of sorts for the tobacco industry. They were, however, blows that the cigarette industry could successfully weather because they were all directed against the smoker himself. While the overwhelming majority of the public has been convinced by the anti-smoking forces that smoking is dangerous to the smoker's health, this has not persuaded very many smokers to give up smoking.
>
> The anti-smoking forces' latest tack, however—on the passive smoking issue—is another matter. What the smoker does to himself may be his business, but what the smoker does to the non-smoker is quite a different matter. . . .
>
> *This we see as the most dangerous development to the viability of the tobacco industry that has yet occurred* [emphasis added].

In short, while the tobacco industry's advertising campaign has done a good job of helping smokers repress the knowledge of what they are doing to themselves and of creating a social environment conducive to smoking, growing awareness of the harmful effects of involuntary smoking threatens to change the social environment so key to promoting their products.

There is a strong scientific consensus that involuntary smoking has adverse effects on children of smokers and people who have existing disease and that smoking produces many irritating subclinical effects such as headache and burning eyes.[5,6] These results have been discussed and are slowly creeping into the public consciousness. Lung cancer, however, has such a strong emotional impact that when Hirayama published his first work, it became a major news story. This broad media exposure of an emotionally powerful result is doubtless what prompted the Tobacco Institute to undertake its unprecedented advertising campaign specifically attacking Dr Hirayama's work.

(Glantz SA: What to do because evidence links involuntary (passive) smoking with lung cancer [Commentary]. West J Med 1984 Apr; 140:636-637)

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The Tobacco Institute took advantage of the fact that the one study that failed to show a statistically significant association between involuntary smoking and lung cancer[4] was conducted by the American Cancer Society. They ignored the author's careful discussion of the limitations in his study—in particular, problems of quantifying exposure to cigarette smoke—and proclaimed that "even" the American Cancer Society had determined that involuntary smoking posed no danger to nonsmokers.[8]

This strategy of systematically trying to undermine the scientific link between smoking and disease is not new. Documents obtained by the Federal Trade Commission[9] show that as early as 1969 one tobacco company had a plan to sow doubt and confusion in the public's mind about the validity of evidence linking smoking to disease and death. The company's document says

> Doubt is our product since it is the best means of competing with the "body of fact" that exists in the mind of the general public. It is also the means of establishing a controversy. If we are successful in establishing a controversy at the public level, then there is an opportunity to put across the real facts about smoking and health.[10]

By emphasizing and playing up areas where there is a genuine controversy about the particular effects of smoking, such as there appears to be in the three studies on passive smoking and lung cancer published in 1981, the Tobacco Institute proposed to cast doubt on the validity of all the evidence.

Much technical discussion that aimed to resolve the differences between the first three studies published in 1981 on involuntary smoking and lung cancer[1,2,4] centered on the question of wives' exposure to secondhand tobacco smoke. The two studies that showed a statistically significant link between involuntary smoking and lung cancer[1,2] were conducted in Japan and Greece where married women stayed home and where very few women smoked, so that the husband was likely to be the only (or, at least, the major) source of exposure to cigarette smoke. The American Cancer Society study was conducted in the United States where women were more likely to work or have other activities outside the home and, hence, more opportunities to be exposed to secondhand smoke. It has been speculated that this difference in exposure accounts for the differences in the results.

Miller's article in this issue of the journal supports this contention and helps to resolve the difference between these three studies. He examined all cancer deaths among nonsmoking wives in northwestern Pennsylvania and found that being married to a smoker increased the risk of dying of cancer. If he examined *all* wives, including wives who worked outside the home, the apparent risks associated with their spouses' smoking fell. This work, combined with a new American study[3] that shows a significant association between involuntary smoking and lung cancer, continues to strengthen the case that involuntary smoking is linked with lung cancer in nonsmokers.

As with lung cancer in smokers, the precise biochemical mechanisms through which the carcinogens in tobacco smoke actually produce disease may never be fully understood. Nevertheless, the evidence at this point is enough to support the National Academy of Sciences' conclusion that "Public policy should clearly articulate that involuntary exposure to tobacco smoke has adverse health effects and ought to be minimized or avoided where possible."[5]

What can individual physicians do to act on this evidence? There are several simple, inexpensive steps that can be taken to protect nonsmokers from the adverse health effects of involuntary smoking and to create an environment that discourages smoking:

- Do not permit smoking in your office, clinic or waiting room.
- Recommend that hospitals at which you practice do not place nonsmoking patients in rooms with smokers. (Some leading medical centers, including the Stanford University and those associated with the Mayo Clinic, have essentially banned smoking.)
- Help nurses and other hospital staff secure smoke-free work areas.
- Recommend that hospitals at which you practice end the sale of cigarettes. (About 70% of American hospitals have already taken this step.)
- Support legislative efforts to protect nonsmokers in the workplace and public places. (Several states and 21 cities and counties within California already have such legislation.)

As the Tobacco Institute fears, these simple acts will not only discourage smoking and help smokers who wish to quit but, more important, will protect and reward the majority who act intelligently and choose not to smoke.

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Special Article

Speculations on the Impact of Prospective Pricing and DRGs

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Medicare's new Prospective Payment System (PPS) has probably generated more speculation about its potential impact than any other recent development in health care. There is almost universal consensus that PPS will have a major influence on the delivery of health care, but there is also relatively little hard evidence on which to predict what direction that influence will take. For example, the New Jersey all-payer system, on which PPS is loosely based, has been in operation only since 1980; furthermore, there are enough major differences between the two programs to make it risky to generalize from one to the other. Health maintenance organizations (HMOs) have used prospective pricing for years, but their experience is also inapplicable to noncapitated prospective systems. Thus almost any prediction about the influence of PPS must be at least somewhat conjectural.

The end product of the health care system is services to patients, so in the long run it probably will be patients who feel the strongest impact from prospective pricing. However, the major impetus for prospective pricing comes from third-party payers' declared or expressed desire to contain their costs and is carried out by influencing the incentives of providers. This report traces the progression from a payer's (in this case, Medicare's) objectives through providers' behavior to their influence on patients.

Impacts on the Payer

Prospective pricing stems mainly from the payer's objective of controlling health care costs. (Although prospective pricing is intended merely to slow the nationwide rate of growth in costs to the payer, rather than to achieve a reduction in absolute cost levels, high-cost providers will nevertheless experience actual declines in amounts paid over the course of the phase-in period.) The mechanism is the setting of limits on particular units of service (payment units) and placing providers at risk for costs they incur over that limit. In prospective systems the price is based on some measure of providers' costs. Thus, over time the "ceiling" effect of the price should depress the rate of cost increases and be reflected in later prices.

Cost Containment

A basic question about prospective pricing is whether it achieves its cost containment objective. Evidence from states with *all-payer* prospective systems indicates that hospital prices there increase more slowly than they do in the rest of the country.* It is important to note, however, that under all-payer systems (as opposed to the single-payer PPS), hospitals must reduce costs because they have little opportunity to shift them from one payer to another.

There are other related questions as well. Does cost containment for inpatient services generate increased outpatient utilization and cost? Does reduction of inpatient service and length of stay lead to cost-ineffective readmission or complications during the stay? Can "gaming" or manipulation of the system actually increase net cost over what it would have been under cost-based reimbursement? It will take some time to find the answers to questions like these.

Cost Shifting

For payers, the most important implication of prospective pricing is that any payer not included in the system can become a victim of cost shifting. A hospital that cannot break even on a prospective rate from one payer will seek to recover the loss from other payers. Medicare's PPS, for example, may well cause hospitals to shift costs to private-sector payers.

The threat of increased cost-shifting may lead payers to press for state-level all-payer systems such as New Jersey's. Such systems promote a degree of equity among payers by imposing uniformity in the formula for determining the prospective rates. They may not

*New Jersey had lower than average hospital cost inflation before implementation of its prospective system, and that gap has widened since. However, there is no empirical evidence linking the reduced inflation rate to prospective pricing.

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ABBREVIATIONS USED IN TEXT

DHHS = Department of Health and Human Services
DRG = Diagnosis Related Group
FAH = Federation of American Hospitals
HMO = health maintenance organization
LOS = length of stay
LTC = long-term care
PPS = Prospective Payment System
PRO = (Utilization and Quality) Peer Review Organization
PSRO = Professional Standards Review Organization
TEFRA = Tax Equality and Fiscal Responsibility Act of 1982

necessarily result in exactly the same rate for all payers, but will be closer to that objective than if some payers enjoy the advantages of prospective pricing and others do not. The PPS legislation, PL 98-21, may make it easier for states to establish their own all-payer systems. It sets forth criteria for such systems that, if met, obligate both Medicare and Medicaid to participate. This feature of the law reflects the view of the Department of Health and Human Services (DHHS) that prospective pricing contains costs only if it prevents cost shifting by including several payers.

There is some evidence that private-sector concerns over cost shifting under PPS will lead to more all-payer systems. Since passage of PL 98-21, three additional states have created hospital rate-setting commissions, and similar legislation was introduced in seven others. (Seven states already regulate hospital rates—four include Medicare under waiver, while the remaining three systems are restricted to private-sector payers.) As more hospitals come under PPS, the increasing cost shift may accelerate the passage of all-payer legislation in other states as well.

The assumption that PPS will increase cost shifting is challenged by some, notably the Federation of American Hospitals (FAH). FAH, the association of investor-owned hospitals, states that PPS will reduce costs to all payers without a formal all-payer system. The reasoning behind their argument is that in order to break even under PPS a hospital will have to make cost-cutting changes—for example, in staff productivity—that will apply to all patients, regardless of payer.

At present there is little concrete evidence to support the FAH argument, but until now there has been no way to test it empirically. As data begin to accumulate from hospitals under PPS, it should become evident whether the program is helping or hurting private-sector payers. The issue of cost-shifting may become academic if a national all-payer system is developed. Senator Edward F. Kennedy (D-Mass) and Congressman Richard Gephardt (D-Mo) are currently working on such a plan as the basis of a unified Democratic party strategy for cost containment. The program would exempt HMOs and states with their own all-payer systems. For Gephardt, this activity apparently signals a shift away from the "competition" approach.

Price Competition

Depending on the way it influences cost shifting, PPS may increase or decrease price competition among payers. If PPS increases cost shifting, larger private-sector payers will be more readily able to pass along these costs, in turn, to smaller ones. This would result from the larger payers' relatively greater ability to negotiate discounts from hospitals. Thus, the larger, stronger payers will enjoy a cost advantage that can be turned into a price advantage as well.

On the other hand, if the Federation of American Hospitals' argument is correct or if all-payer state systems reduce cost-shifting, the relatively stronger negotiating position of large payers will be weakened. The increased equity among payers in terms of cost will tend to reduce the cost advantages that can be exploited in price competition. This in turn should decrease price competition among payers.

Using national Diagnosis Related Group (DRG) values, PPS will also redistribute hospital revenues geographically from high-cost areas such as California and New England to low-cost areas like the South. A nationwide all-payer system, if structured like PPS, would reduce the influence of regional differences among carriers. Translated into costs to payers, the redistribution of hospital revenues means that regional or local payers in formerly high-cost areas will now find their costs reduced, while those in formerly low-cost areas will find theirs correspondingly increased.

Utilization Review/Quality Assurance

Under any prospective system, utilization review takes on added importance. The balance between overutilization and underutilization is critical, and utilization review is central to maintaining that balance. It produces the information a hospital needs to keep costs below the revenue ceiling while providing a high enough level of care to minimize malpractice liability.

The Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA) changed the hospital utilization review system for Medicare in ways that may increase the influence of DHHS over the process. The old Professional Standards Review Organizations (PSROs) are to be replaced by Utilization and Quality Peer Review Organizations (PROs). The differences between the two types of organizations are significant for both the provider and the payer.

From the government's point of view, the two most important changes are that (1) PROs will operate under performance-based contracts, committing themselves to meet contractually agreed upon reductions in utilization and (2) after the first year it will be possible for fiscal intermediaries to sponsor PROs. Initially, physician-sponsored groups will have preference in obtaining PRO contracts and will have a strong incentive to meet utilization-control targets in order to keep their contracts. Whether they succeed or forfeit the contracts to other groups, the government as payer will benefit from the new system.

As will be noted below, the change in utilization

review has a strong potential impact on providers as well.

These three general implications—a trend toward all-payer systems, changes in the competition among payers and payers' increased control over utilization—are by no means the only changes that can occur from PPS, but they illustrate the kind of impact it will have on payers.

Impact on Providers

Prospective pricing is intended to achieve its cost containment goals by modifying provider incentives, so it is not surprising that attention has focused on the types of impact the new system will have on them.

Hospital-Physician Relations

Probably the most obvious implication of PPS is that it will force hospitals and attending physicians to cooperate much more closely in holding down utilization. Under cost-based reimbursement, a hospital benefited financially from a physician who utilized its services heavily; the more cost-generating services he or she ordered, the more revenue the hospital obtained. Today, under PPS, that same physician is viewed as a threat to the hospital's survival; unless his practice patterns keep utilization at or below the price ceiling, the hospital can lose money.

In the hospital-physician relationship, each side must balance conflicting incentives. By training and experience the physician is inclined to use any diagnostic or therapeutic service that potentially can help the patient. This inclination is bolstered by the threat of professional liability which results in "defensive" medicine—doing "everything possible" for the patient and thereby minimizing the risk of being sued for failure to provide adequate care.

This pressure on physicians to introduce and make heavy use of hospital services is countered by the realization that their hospitals of choice are at risk for any costs over and above the DRG revenue cap. Those costs that cannot be shifted or eliminated must be absorbed and over the long run can threaten the hospital's survival. For a physician this fact raises a major concern: the loss of his or her hospital of choice as a practice setting and the potential difficulty in joining the staff of another suitable hospital. This concern is becoming more relevant as increasing numbers of hospital medical staffs are being closed to new members.

A hospital faces the same conflicting incentives. To remain competitive, it must be able to attract admissions while at the same time holding utilization (and costs) below the revenue ceiling. Like physicians, a hospital increases its liability risks by underutilization. It also knows that a competing hospital that successfully shaves costs closer to the bone will be more profitable. Competitive pressures no longer can be relieved by increasing investment and utilization, and internal conflicts may make it potentially more difficult for hospitals and physicians to reach the necessary accommodations between themselves. Unless there is greater accommodation between physicians and hospitals, however, these internal conflicts will prevent them from operating successfully under PPS. There has to be a mutual recognition of both the physicians' and the hospitals' imperatives. If either side tries to impose its will unilaterally on the other, both will lose.

Data Management

The physician-hospital cooperation required by PPS will depend largely upon the ability of both parties to understand and rely on the hospital's utilization data management system. Given that most hospitals and physicians have limited experience with the type of data base involved, this may require something of an act of faith on both their parts.

Although formal assignment of a case to a particular DRG will be done by the fiscal intermediary, hospitals will need to be able to replicate that process themselves. It is essential to know, as early after admission as possible, how much the hospital will be paid for a particular case. The hospital must choose among vendors of case-mix software, many of which themselves have limited experience in this area. The data base will be only as good as the medical records and billing data merged into it. Thus, the hospital must also rely on the physician and on its own internal recordkeeping. The physician, in turn, must rely on the PRO that will use the data to make judgments about his or her practice patterns.

This heavy reliance on relatively new types of data places substantially greater power in the hands of those who generate and manage the data base. These include at least the review nurse, the physician who is responsible for the completeness and accuracy of the medical record, the medical record administrator, the cost analyst in the business office and the data processing manager. Each of these people will command new leverage in dealing with other players in the system. They will be able, over time, to influence the operation in ways that facilitate and emphasize the gathering and use of the information they control. In other words, data-base management will become something of an end in itself as it becomes more crucial to achieving other hospital objectives.

Capital Allocation

There is a consensus that prospective pricing will reduce or retard capital expenditures by hospitals. Under traditional cost-based reimbursement, capital costs could be passed through to the payer, so there was little incentive to control the amount of capital investment or the cost of money. Under PPS, however, capital costs (after the phase-in period) will have to be covered by the DRG payment. New technology is accommodated by PPS in only limited ways; one percentage point is added to the hospital "market basket" inflator for technological upgrading, and DRGs are to be reexamined at least every four years, partly to determine whether the spread of new technology has rendered any classification obsolete.

Capital investments usually will have to show po-

tential to generate a net savings to the hospital. Moreover, the cost of capital itself can be expected to increase. Not-for-profit hospitals tend to rely heavily on bonded indebtedness, and their bond ratings will deteriorate if their operating margins are reduced by prospective payment. For-profit hospitals derive more of their capital from the sale of stock, but reduced profitability and new Medicare limits on allowable return on equity may make them less attractive to investors. Profitability will be especially affected by the fact that prospective pricing discourages utilization of ancillary services: under cost-based reimbursement, proprietaries earned substantially more margin on such services than did not-for-profits.

It has been said that the capital squeeze will hurt for-profits more than not-for-profits. The loss of profits from ancillary services is cited as one reason; another is that not-for-profits have more "fat" to trim from their staffing patterns. If a recent legislative proposal passes, proprietaries will also be severely restricted in access to the Industrial Development Bond market.

The other side of this argument is that for-profit hospitals will maintain their competitive advantage because of their location (mainly prosperous suburbs of growing cities in loosely regulated sunbelt states), payer mix (low proportions of Medicare/Medicaid and bad debt), case mix (emphasizing elective surgical procedures) and management efficiencies (tight staffing, large-scale purchasing). This could give them easier access to capital markets.

It remains to be seen whether proprietaries will suffer more than non-profits from reduced access to and increased cost of capital. For that matter, it is not clear that the net effect of reduced investment will necessarily be negative. One analysis has shown that every dollar of hospital capital investment generates $1.84 in added operating costs. For a hospital whose profit-maximizing strategy now must rely more heavily on reduced costs, capital investment will be much less attractive than in the past.

Organizational Structure

Prospective pricing can be expected to change the corporate structures of hospitals. Two changes in particular seem likely to become widespread.

First is corporate restructuring of autonomous not-for-profit hospitals. There will be much stronger incentives for those institutions to form foundations, umbrella corporations or other entities that can engage in for-profit business without jeopardizing the tax-exempt status of the hospital itself. Such entities not only can generate added revenue but also can raise capital by selling stock. Other uses of restructuring are to form chains from independent units and to facilitate shared services (group purchasing, for example).

A second likely type of organizational change will be vertical integration. Acute care hospitals will seek to gain control over long-term care (LTC) facilities either by purchases, lease, construction, partial relicensure ("swing beds") or some other method. The incentive to do so comes from the relative shortage of LTC beds, combined with the revenue ceiling under PPS. Under the old cost-based reimbursement system a Medicare patient may have been ready for transfer to an LTC facility, but if an LTC bed was unavailable the acute-care hospital was not reimbursed for the waiting days. Under PPS, there is even stronger pressure to reduce acute-level length of stay so it will be increasingly important for the hospital to control access to a supply of LTC beds. Arranging such a relationship with an LTC facility will be easier for a hospital that has undergone corporate restructuring and has an appropriate entity in place to connect the two institutions.

Specialization by DRG

There is some evidence that as a hospital learns which services are profitable for it to provide, it will seek to maximize use of those services and avoid "loss leaders" or unprofitable services. This is more likely to occur under an all-payer system, but could apply to PPS as well. A relatively simple method for doing so is to employ the preferred provider concept. Once a hospital has identified its profitable services (or DRGs within a service) it offers a discount on them (at a still-profitable level) to third-party payers (in this case, Medicare). Tied to this contract may be some obligation for the payer to steer patients elsewhere for money-losing services. At present such a practice would be illegal in some states, but specialization has begun to appear on a small scale in New Jersey.

Selective contracting by DRG would be attractive to a hospital if (1) its most profitable DRGs could bring in enough patient volume to meet its revenue needs and (2) there were little competition from other hospitals for the same DRGs. In practice, however, a DRG can be extremely profitable on a per-case basis, while being limited to one or two cases per year. Moreover, a particular DRG that is profitable for one hospital may well be even more so for its competitor across town. Finally, the surplus of beds in many highly competitive markets may make specialization a luxury that hospitals cannot afford. For those hospitals it will be necessary to do just the opposite—to offer every service they can in order to "capture its contribution" to fixed costs. The reasoning here is that as long as the payment exceeds the variable costs of providing a service, it should be provided (as long as there is unused capacity) because it is also making some contribution to covering fixed costs. Given the high ratio of fixed to variable costs in hospitals and the unused capacity available in many institutions, the need to recover fixed costs will make specializations by DRG impractical for many of them.

Medical Staff Relations

The shrinkage of capital and possibility of DRG specialization have implications for relationships within a hospital's medical staff. Different departments within the staff now will have to compete more directly with each other for capital and other hospital resources. Just as the hospital will identify individual physicians who

generate a net cost or profit, the same will be true of entire services. Capital and other resources (such as bed capacity and operating room time) will flow to those services that can show they will use such resources more profitably than other departments or services. It will not be enough just to show that a new technology or other investment for use by one medical staff department will generate net savings or profit; it must generate greater savings than could another department's use of the same funds.

In the past this form of competition has been minimized by a number of factors. Both the capital costs and increased operating costs associated with a new technology or other investment could be passed through to payers. There was also the danger that competing institutions could lure admissions away by providing the same new service. These factors, working together, encouraged a hospital to invest in technology regardless of its cost-effectiveness. Some investments in new technology were acknowledged loss leaders to attract lucrative admissions or generate billable ancillary services.

Obviously no hospital has access to unlimited capital; however, there were fewer constraints against investment under the old system, so potential conflict over limited resources was reduced by making more resources available. When conflict could not be avoided that way, internal politics within the medical staff often dealt with it informally. Both of these options are severely limited under PPS.

Utilization Review

The impacts of changes in utilization review on the payer have already been noted. These changes will have an even stronger influence on hospitals and physicians.

First, PROs can be expected to be more aggressive than the old PSROs in terms of utilization control. Some PROs will be for-profit entities, and all of them will have an incentive to meet their contractual targets for reducing admissions under certain DRGs.

Second, utilization review will produce the data that will pinpoint the DRGs and individual physicians who generate profits and losses for the hospital. This will be invaluable to a hospital in its strategic planning, but will place a great deal of pressure on a physician whose practice pattern (or, perhaps, specialty) represents a net cost to the hospital.

Third, the focus of review will now be much broader. Under cost-based reimbursement, the payment unit was the individual billed services (one day's inpatient room charge, an individual medication and the like), so utilization review was concerned with the appropriateness of the individual service. Under PPS, the payment unit is the admission, so utilization review will be concerned with the appropriateness of the admission and of the DRG to which it is assigned.

Finally, utilization review is the physician's first line of defense in resisting pressure to curtail services. In addition to its traditional role of policing overutilization, it will now be responsible for preventing *under*utilization as well.

DRG Pricing and Payment

The method of calculating the payment rate for each DRG probably will have stronger impact on providers than any other element of the system. This impact will not be fully felt until the end of the three-year phase-in period, but it can be easily anticipated already.

Perhaps the major single effect is the imposition of national urban and rural rates for each DRG. High-cost hospitals will lose all the money that low-cost hospitals will gain. Some entire regions, such as California or New England, will find most of their PPS hospitals suffering reduced reimbursement. These hospitals and, by extension, the markets they serve, will have reduced access to capital, greater risk of closure and, probably, a gradual emigration of health care professionals. Conversely, low cost hospitals and those in low-cost areas will have improved cash flow, access to capital and a larger pool of qualified personnel. These effects will be strongest in the early years after the end of the phase-in period.

Of course, under PPS these effects will be felt only to the extent of Medicare involvement and they would probably be lessened by state all-payer systems. Nonetheless, regional redistribution of some 36% of hospital revenues will be a major change for both the winners and losers. There are other sorts of impact of the payment system as well. At present, for example, the PPS phase-in calls for retention of the urban-rural wage differential. This can create anomalies in areas where "rural" and "urban" hospitals must compete for the same workers. Similarly, several data elements in calculating the reimbursement formula will be changed on October 1 of each year during the phase-in period—this despite the fact that some hospitals' PPS years begin as late as July 1.

Some effects cannot be predicted beyond the phase-in period. For example, the method of integrating capital costs into the DRG rate formula has yet to be determined. Some methods, like the flat percentage add-on recommended by the American Hospital Association, would tend to help institutions in the Northeast at the expense of those in the South. This would presumably occur because institutions in the South now spend more on capital investments relative to revenue than those in the rate-regulated states of the Northeast.

Gaming

Any system that is not absolutely rigid can be manipulated. There are a great many actions a hospital can take to maximize reimbursement under PPS. Some of these will be discussed in terms of their effects on patients, but two forms of "gaming," or manipulation, are particularly relevant here: DRG "creep" and unbundling.

DRG creep involves the subtle shift upward from lower-cost categories to higher-cost ones. At some levels DRG creep is an ethical tactic. If a patient has two or more equally valid conditions that might be listed as principal diagnosis, it is legitimate to select the one that leads to the higher-paying DRG. On the other

hand, it would be unethical to select the principal diagnosis strictly on the basis of its DRG value.

Unbundling involves divestiture of hospital functions (such as laboratory or radiology facilities) in order to minimize the costs that must be covered by the DRG payment. This, too, would be unethical, and a large portion of the PPS regulations is devoted to preventing it.

Impacts on the Patient

Hospitals and physicians are in the business of providing health care, not gaming PPS, and the impacts of PPS on patients must be viewed in that perspective. Granted, every hospital must generate an operating surplus; for nonprofit institutions, the main reason is to be able to continue offering hospital care, and in a sense the same is true of many investor-owned institutions as well. They are profitable in part because there is a market niche (that is, sufficient ongoing demand for health care) that makes them more profitable than alternative uses of the same capital. In that context, there are a number of ways in which patients will be affected by hospitals' efforts to maximize profit under PPS.

Length of Stay

DRGs rely on length of stay (LOS) as a surrogate measure of resource use. It is therefore likely that hospitals will look to reducing LOS as a major source of savings. Under PPS, restricted to Medicare, this approach makes more sense than for other payers. While a typical patient's costs are concentrated early in the hospital stay, those of Medicare patients are more evenly spread over the course of the stay.

The strictly economic incentive to reduce LOS is strongest in areas with the highest per-diem costs. Unfortunately, some areas with high per-diem cost, such as California, already have shorter LOS than others. Thus it will be difficult to reduce LOS further without jeopardizing the patients' treatment outcome. The New Jersey Medical Society is investigating a group of post-discharge deaths in that state to determine whether discharge was premature in those cases.

LOS can also be manipulated by transfer. If the second hospital is also under PPS, as is most often the case, it receives the DRG payment and the first hospital is paid a prorated per-diem rate. Thus if the first hospital can make money at the per-diem rate, it behooves it to hold patients as long as possible before transferring; otherwise, it will want to transfer them as early as possible.

Another variation is readmission. If a patient could be admitted under either of two diagnoses, it may be possible to admit and quickly discharge him under one of them, collect the DRG payment for that stay, and then readmit under the second diagnosis.

Clearly, any manipulation of LOS will be subject to strict Peer Review Organization scrutiny and it will be difficult for a hospital to abuse it on a large scale. Nevertheless, to the extent it does occur, it can affect the quality of care.

Ancillary Services

Another area of savings will be reduced use of ancillary services. Redundant or "backup" diagnostic procedures will be reduced, placing a premium on the accuracy of those carried out. Similarly, therapies that cannot be shown to be cost effective may be eliminated, even if marginally beneficial to patients.

More significant, however, new diagnostic and therapeutic technologies will be much more slowly adopted than in the past. The requirement that it generate a net savings will become the test of virtually every new technology. Given the increased cost of capital in the future and new technology's greater burden on operating costs, this will be a formidable hurdle indeed. Furthermore, the competitive pressure to adopt new technology is reduced by the fact that a hospital's competitors are in the same situation. It seems reasonable to assume that over time there will be a ripple effect backward from the medical technology marketplace to research and development. As demand slows, so will the rate of new product development.

Availability of Care

Research indicates that a hospital's chances of survival have little to do with management efficiency. No matter how good a hospital is at reducing controllable costs, its fate is likely to be determined by factors beyond its control. In practice this means, unfortunately, that the hospitals that are most threatened are those serving people who have nowhere else to go. Two categories are especially vulnerable: inner-city and rural public hospitals.

The main threat to these hospitals is the burden of unreimbursed or underreimbursed care. As the last resort source of care, county hospitals carry a heavy Medicare/Medicaid and MIA (medically indigent adult) caseload at less than full-cost payment, as well as largely unpaid care of indigents who are not covered by government programs. Because of location and/or competition from private institutions, they cannot attract sufficient insured or self-pay patient loads to make up their deficits. Inner-city hospitals suffer further from high operating costs (such as for labor and security), while rural institutions often have insufficient volume to spread costs adequately.

While these problems are most severe for the types of hospitals described above, they affect others as well. Autonomous nonprofit hospitals in particular, with Hill-Burton or corporate charter obligation to provide charity care, are vulnerable even in relatively prosperous areas.

Prospective pricing can be expected to aggravate this problem in high-cost areas. The impact of PPS will depend on how large a private-sector caseload a hospital has in order to accept the shifted costs. The ability to shift Medicare costs becomes more crucial under the PPS revenue cap than under cost-based reimbursement,

so the hospital that lacks a large private-sector caseload is now in an even worse position if it is unable to bring its costs below the DRG rate caps. For a patient in such a hospital, this can mean more severely reduced services than in others or possibly eventual closure of the only source of care. Either way that patient will feel the impact of the new system more sharply than patients in stronger hospitals.

Regional differences will also appear, at least in the years just after the switch to the nationwide DRG rate. Even the most stressed hospitals in low-cost regions will feel some relief as revenues, at least on a regional basis, exceed costs. Conversely, even the relatively secure institutions in high-cost areas will be strained to cover costs, and those already in trouble will be even more so.

Out-of-Pocket Costs

Increased future patient cost-sharing is virtually inevitable under any payment system. Under PPS, the Medicare cost shift will accelerate this trend. Further, the "budget neutrality" requirement during the phase-in will likely lead to some cost-shifting, although the impact of this may not be felt immediately. For example, DHHS includes a "fudge factor" to allow for the effects of gaming. However, if the TEFRA target is not met in one federal budget year, the difference will probably be made up in succeeding years by reducing the DRG rate.

Summary

Prospective pricing seeks to reduce costs by changing provider incentives. By setting payment ceilings and letting providers know what those ceilings are, the system sets cost-control targets that a provider must meet over the long term.

Equipped with this knowledge, a hospital must seek cooperation from physicians, who typically control about 70% of hospital costs. Physicians must balance the patients' quality-of-care needs with the hospital's economic viability.

The effects of cost-containment efforts by payers, implemented by providers, are distilled in their impacts on patients. There are strong incentives for providers to reduce services and length of stay, and it will be some time before it becomes clear how much this will affect the quality of care. For some patients, however, the more immediate issue will be whether any care is available at all, regardless of quality.

Public Policy Review

A Ten-Year Progress Report on a Family Practice Residency Network in Northern California

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We are now beginning to be able to evaluate the results of the rapid growth of family practice residency training programs during the past decade. Because this growth has been supported by federal and state funds, it is particularly important to review these programs to measure their progress toward the public policy goals established by legislation. The University of California, Davis, School of Medicine has been an innovator and leader in training family physicians. Graduates of the UC Davis Network of Family Practice Residency Programs are locating in medically underserved areas and are helping to respond to the perceived problems of specialty and geographic maldistribution of physicians.

(Davidson RC, Fox J: Public policy review—A ten-year progress report on a family practice residency network in Northern California [Medical Education]. West J Med 1984 Apr; 140:645-649)

During the past 15 years, a major United States health policy goal has been to increase the number of physicians who choose a career in primary care—specifically, family practice, general internal medicine and general pediatrics.[1-3] Federal support of medical education via capitation payments, though no longer available, was tied to a requirement of increasing the number of primary care physicians.[2] Direct federal support of primary care training programs has come in the form of grants for the development of academic departments of family medicine, graduate and undergraduate training in family practice and graduate training in primary care internal medicine and pediatrics. The national Area Health Education Center (AHEC) program has also supported primary care physician training through its unique and highly successful incentive program that uses a community priority-setting mechanism for determining program priorities.[4] State funding of family practice education has also assisted the growth of this specialty. In all, 23 states now directly support family practice educational programs.[5] In California the Song-Brown Family Physician Training Act supplies financial support of family practice education as well as the education of family nurse practitioners and physician assistants.[6]

This public support of family practice training grew out of perceived needs for a change in the type of physicians being trained. The Millis, Willard, Pellegrino and Folsom reports in the 1960s clearly elucidated this national need.[7-10] Two of the major issues described by these authors were the lack of an adequate number of physicians to function as the primary providers of ongoing services to persons and families, and a geographic maldistribution of physicians with large rural areas being significantly medically underserved.

During the past 12 years, with the financial assistance of government funding sources, a tremendous growth has occurred in the training of physicians specializing in family practice. There are currently academic departments or divisions of family medicine in 114 of the nation's 130 medical schools.[11] According to data supplied by the American Academy of Family Physicians, as of July 1982 there were 387 approved residency programs in family practice with 7,200 residents in training.

New public policy programs in medical education take at least a decade and, more commonly, two decades until the results of the new policy can be measured for its impact. The process of medical education takes an average of eight years from entrance

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Figure 1.—University of California, Davis, family practice residency network.

Figure 2.—California communities with one or more University of California, Davis, family practice graduates.

TABLE 1.—*Graduates of the University of California, Davis, Family Practice Network Per Year by Program*

Program Location	*Academic Year* 1972-1973	1973-1974	1974-1975	1975-1976	1976-1977	1977-1978	1978-1979	1979-1980	1980-1981	*Total*
Sacramento	1	7	5	8	8	10	10	12	11	72
Stockton	..	..	..	5	5	6	5	6	6	33
Merced	..	..	..	3	5	4	4	3	6	25
Redding	..	..	..	..	3	4	4	4	4	19
Martinez	..	..	..	..	6	6	6	6	6	30
Modesto	..	..	..	..	..	5	4	6	5	20
TOTALS	1	7	5	16	27	35	33	37	38	199

to medical school until that cohort of physicians begins to enter practice. Thus, it is timely to review the progress of primary care training programs toward meeting stated public policy goals.

We review the progress of the University of California, Davis, Network of Family Practice Residency Programs. These programs receive both federal and state support. The network has developed over the past 12 years into a major provider of family physicians for central and northern California. A 1974 article by Geyman and Brown described this developing regional network of Family Practice Residency Programs.[12] The goals and objectives of the network were similar to the national goals enumerated in the initial policy papers.[7-10]

Development

The UC Davis School of Medicine was founded in 1968 and admitted its first class of students that same year. The Department of Family Practice was established in October 1970. The first residency training program developed by the department began in July 1971. This program was located in what was then the Sacramento County Hospital. The university subsequently purchased the hospital and clinics and the facilities are now known as the University of California Davis Medical Center, Sacramento.

The network developed over the ensuing years to its current size of six programs (Figure 1) and 117 residents. The second residency program to join the network began in July 1973 at the San Joaquin General Hospital in Stockton. The following year, the Merced Community Medical Center program began, followed in July 1975 by the program at Shasta County Hospital in Redding. The Merced and Redding programs are integrated with the University Medical Center in Sacramento. Residents in these programs spend the first year of training at the University Medical Center in Sacramento and complete their second and third years at the respective community hospital. Contra Costa County Hospital in Martinez joined the network in 1976 when a previous two-year general practice residency was converted to the three-year format of family practice. The final program joined the network in 1977 at Scenic General Hospital in Modesto.

Graduate Follow-up

To evaluate the outcome of this network, a graduate follow-up study was done. The study population consisted of all graduates of the network from inception through the graduating class of June 1981. There were 199 graduates during this time period. Table 1 shows the network production of graduates by year and by program. The survey instrument used was a mailed questionnaire that elicited information on practice characteristics, hospital privileges, practice location and an evaluation of the training received in residency as preparation for practice. To allow comparisons, portions of the survey instrument were identical to similar surveys of family practice residency graduates in networks in Minnesota,[13] Virginia[14] and Washington.[15] By repeat mailings and telephone contacts by faculty to nonrespondents, 177 completed surveys were returned for an 89% response rate. A review of nonrespondents showed no pattern by program or year of graduation so it was assumed that the respondents adequately reflect the experience of all graduates. Thus, references in this article are to graduates rather than respondents.

TABLE 2.—*Size of Community of Practice Location of University of California, Davis, Family Practice Graduates*

Size of Community	*Number Graduates*	*Percentage*
Under 2,500	6	3
2,500-24,999	60	35
25,000-49,999	27	16
50,000-99,999	16	9
100,000-499,999	34	20
500,000 or more		
Central city	12	7
Suburbs	18	10
No response	4*	..
TOTALS	177	100

*Not included in percent compilation.

Of the graduates, 70% are practicing in California. Figure 2 shows the communities in California in which one or more graduates are located. Many locations have more than one graduate practicing in that location but are represented by only one dot.

The sizes of the communities in which the graduates are located show a pattern of preference for communities of small to medium size. Table 2 shows the distribution of the sizes of the communities in which the UC Davis Network graduates practice. About 69% of the graduates have been in the same location since graduation while 31% have moved one or more times.

The type of practice selected by the graduates shows

TABLE 3.—*Predominant Mode of Practice of Graduates of the University of California, Davis, Family Practice Network*

Practice Type	*Number Graduates*	*Percentage*
Solo, fee for service (FFS)	42	24
Partnership, FFS	24	13
Single-specialty, FFS group	25	14
Multispecialty, FFS group	19	11
Health maintenance organization	14	8
Teaching/medical school	2	1
Teaching/community hospital	6	3
Military	1	1
National Health Service Corps	2	1
Emergency room	22	12
Continuing training	3	2
Other	17	10
TOTALS	177	100

TABLE 4.—*Summary of Hospital Privileges of University of California, Davis, Family Practice Graduates*

Hospital Privileges	*Number Graduates*	*Percentage of All Graduates*	*Percentage of Graduates With Hospital Privileges*
Adult medicine	160	90	100
Pediatrics	154	87	96
ICU/CCU	136	77	85
Right heart catheterization	16	9	10
Pacemaker placement	16	9	10
Routine obstetric care	117	66	73
Complicated obstetrics	58	33	36
Cesarean section	37	21	23
Surgery, first assistant	131	74	82
Minor surgery	96	54	60
Major surgery	11	6	7
Emergency room only	2	1	N/A
No hospital affiliation	14	8	N/A

ICU/CCU = intensive care unit or coronary care unit, N/A = not applicable

a preference for group or partnership arrangements, though 24% opened a solo practice (Table 3). When graduates identified a mix of types of practices, they were categorized by their major practice type. In all, 62% use fee-for-service as the major payment mechanism for their practice.

The graduates were asked a series of questions regarding their scope of practice and hospital privileges. Their hospital privileges are summarized in Table 4. When asked about their impressions of the adequacy of their hospital privileges, 90% of the graduates indicated their range of privileges was about right and 10% responded that the privileges were too restrictive. Also, 15 graduates (8%) stated they had at least one requested hospital privilege denied.

Although 73% of the graduates had hospital obstetric privileges, only 56% were currently accepting obstetric patients. Another 26% stated they previously had accepted obstetric patients but were no longer doing so.

Regarding the use of mid-level practitioners, 35% of the graduates currently include family nurse practitioners or physician assistants in their practices. Another 12% stated they are not currently using nurse practitioners or physician assistants but plan to in the future.

When asked about teaching activities, 52% of the graduates stated they currently have a faculty appointment and an ongoing teaching relationship with a family practice program. Of those teaching, 59% were involved with UC Davis-sponsored or affiliated programs while the remainder are faculty of programs affiliated with other medical schools. Their teaching activities were fairly evenly split between instruction of medical students, family nurse practitioner or physician assistant students and family practice residents.

Discussion

An analysis of the results of this public policy initiative must measure outcomes against a set of stated goals. A review of the early literature calling for the development of a new medical specialty called family practice shows several goals that various authors have suggested. Davidson in 1980 suggested five major goals for family practice residency training.[16]

In reviewing federal and state legislation,[1-3] two themes emerge as universal goals. One of these is to reduce the perceived specialty maldistribution of physicians by producing more primary care physicians. Graham calls this the production function.[17] The second is to alleviate the perceived geographic maldistribution of physicians that leaves significant populations in medically underserved areas. Graham calls this the distribution function.[17]

The development of this regional network, like the development of family practice residency programs across the country, has increased the number of family physicians being trained. The report of the Graduate Medical Education National Advisory Council now shows an adequate number of primary care physicians in training to meet national goals.[18] The annual American Medical Association (AMA) study on medical education clearly shows a redistribution of physician specialty career choices when compared with the era before the rapid growth of family practice programs.[19,20] Federal and state funds have helped meet this objective.

The geographic distribution of physicians is a more complicated issue to analyze. Newhouse and co-workers,[21] using national data, suggest that increasing competitive forces are affecting physician practice site decisions and that more physicians of all specialties will choose practice sites away from the traditionally popular areas that are now considered adequately served or overserved.

Graduates of the UC Davis Network of Family Practice Residency Programs have located to a significant extent in areas determined by health planners to be underserved by physicians. When the practice locations of UC Davis family practice graduates in California are measured against the areas designated by the California Health Manpower Policy Commission[22] as medically underserved areas, we find that 31% are in such areas. Other family practice

graduate follow-up studies have shown similar results.[13-15,23,24] It appears that family practice is successfully responding to the problem of geographic maldistribution.

An issue that continually surfaces, especially with medical students who are considering family practice as a career, is the ability of family physicians to obtain adequate hospital privileges. Stern and Black and associates studied this issue on a national basis[25,26] and found significant regional variation. Geyman reviewed the national data available and concluded that less than 4% of hospital privileges requested by family practice residency graduates have been denied.[27] The findings that 90% of the UC Davis network graduates felt their privileges were "about right" and that only 8% had any privileges denied support the contention that residency-trained family physicians can obtain appropriate hospital privileges.

The UC Davis Department of Family Practice has also been an innovative leader in the development of training programs for family nurse practitioners and physician assistants. A stated goal of the department has been to train family physicians in a team practice model so they will continue that mode of practice upon graduation. The finding that 46% of the graduates are currently practicing with family nurse practitioners or physician assistants, or plan to in the future, speaks to the success of this team training mode.

A very positive finding was the large number, 52%, of graduates who are actively teaching in a family practice program. This suggests that the shortage of family practice faculty that plagued the early development of training programs is being overcome.

Summary

This study documents the significant impact that the UC Davis Network of Family Practice Residency Programs is having in California and the western states. Graduates are meeting the public policy expectations regarding family practice. This is especially true in the issue of location of practice.

The future challenge to studies of family practice graduates will be to go beyond the issues of location and scope of practice, to consider such issues as quality of care, content of practice and cost effectiveness of family practice.

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Public Health and Preventive Medicine

Plague—Perspectives on a Rare Disease

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One of a series of articles from western state public health departments

As a result of medical journal articles and media coverage, practitioners are probably aware that plague is enzootic in the American West and that more cases of plague in humans (40) were reported in 1983 than in any single year since 1920 (50 cases with 29 deaths).[1] Because physicians are familiar with the basic epidemiologic and clinical features of *Yersinia pestis* infection or have ready access to this information, I will discuss selected historical, social and scientific aspects of the disease.

The history of plague is highly dramatic, which accounts for the elevation of its name to the symbolic level and to the generic term for pestilence—whether of infectious disease or football team injuries. Several recent books (perhaps reflecting current apocalyptic preoccupations) provide well-written accounts of the Western world's most fearsome plague episode, the Black Death of 1348 through 1351.[2-4] However, the history of plague in our hemisphere is less well appreciated.

The most recent pandemic of plague, which apparently started in China in the mid-1800s, spread to this country via the time-honored routes of trade, in this case commercial maritime activity.[1] As a result, rodent plague was introduced into port cities of the Pacific coast. The first documented human plague case in this country occurred in 1899, diagnosed in a Japanese seaman in San Francisco.[1] By the following year, human cases were occurring among US residents, presumably from exposure to an urban rat-flea complex.[1] From 1900 to 1907, nearly all of the 318 human cases reported in this country resulted from urban plague exposure. Then, in 1908 plague infections acquired from a wild rodent-flea complex were reported from Contra Costa County, California.[1] This signaled a new era in American plague, as the disease moved steadily outwards from port cities into rodent populations inhabiting large expanses of the American West from Montana to New Mexico, and from California to western Texas, Kansas and Nebraska. Accordingly, World Health Organization plague maps now include the entire American West as either a probable plague area or a known focus, along with the more venerable African and Asian foci.

The major initial consequence of this shift from urban-based to sylvatic rodent plague was a decline in reported cases. From 1927 to 1965, an average of only 2.3 cases was reported annually,[5] reflecting the decreased risk of plague acquisition in rural as compared with dense urban settings.

The third phase of plague history in this country began in the late 1960s and has been characterized by an increased number of cases. From 1970 through 1983 there were 195 cases reported, representing an annual average of 13.9 plague cases.

In summary, the port city-urban plague period was succeeded by plague's movement into the rural West, where a small number of cases occurred until the past 10 to 15 years. The essential point in this overview is that plague is a relatively new disease in this part of the world. A corollary is that plague ecology and epidemiology cannot be assumed to be stable. Plague seems firmly established in its American home, but its newness should prevent complacency about our ability to predict its future in this country.

From public information and health education perspectives, plague is a complicated and difficult problem. Each reported case (and particularly the occasional plague death) provokes intense media interest. The regional and national media seem to relish using "plague" and especially "The Black Death" to frighten and titillate. Clearly, the problem with plague from this viewpoint is its name. A name change might block visceral response and thereby help focus on its current

(Mann J: Plague—Perspectives on a rare disease [Public Health and Preventive Medicine]. West J Med 1984 Apr; 140:650-651)

Dr Mann was State Epidemiologist, State of New Mexico Health and Environment Department, Santa Fe, at the time this article was submitted. He is now with the Centers for Disease Control.

Reprint requests to New Mexico Health & Environment Dept, PO Box 968, Santa Fe, NM 87503.

clinical reality—a relatively rare, usually curable but nevertheless serious Gram-negative infection. Specifically, plague in the United States needs what Hansen's disease has accomplished for leprosy. Yersin's disease, after Alexander Yersin, discoverer of *Y pestis*,[6] has been proposed.

Nevertheless, trivializing plague would be inappropriate, for not only is the disease serious for individual patients, but secondary pneumonia can develop in plague patients, thereby creating potential for direct person-to-person transmission of the disease—that is, spread of primary plague pneumonia.[7] International and limited national experience has shown that outbreaks of pneumonic plague can spread rapidly and cause considerable mortality despite medical treatment.[7,8] Interestingly, the proportion of all plague patients with secondary pneumonia seems to have increased from about 5% before 1975[8] to 20% since then.[9] The more frequent occurrence of secondary plague pneumonia, combined with the increased number of plague cases, requires that the disease be seriously considered from a public health perspective. Therefore, while an individual case deserves to be called Yersin's disease, the public health disease of "plague" continues to exist.

Finally, several important scientific issues need further attention, starting with the salient question, Why is human plague so rare? Given enzootic and epizootic plague throughout the West, the very small number of human cases appears paradoxical. Further elucidation of the animal-flea-human complex is needed, with a special focus on the flea-human relationship, because about 85% of cases (New Mexico data) are estimated to be flea-borne. Recent studies of the relationship have found that most cases are acquired in the immediate vicinity of a patient's residence in rural areas, that the presence of "rodent attraction factors" around a home significantly increases the risk of plague acquisition[10] and that some cases clearly result from fleas mechanically transported to the home environment by pet dogs and cats that have not been dusted with flea powder. Nevertheless, the dynamics of the relationship between the disease in nature (animal-flea complex) and humans deserve further study.

A second important research area involves plague pneumonia. The last person-to-person plague transmission in this country occurred during the Los Angeles epidemic of late 1924. Yet, why have no secondary cases of plague resulted from contact with the plague pneumonia patients of the past decade? Despite public health efforts to identify and isolate suspected plague patients, secondary plague pneumonia has occasionally occurred and gone unrecognized and yet plague has not spread. Greater understanding of factors involved in transmissibility could assist control efforts and further quantify the level of risk to public health created by the existence of enzootic plague in our country.

Finally, surveillance of the animal-flea complex in the American West, using sensitive, reproducible and efficient methods, is essential to chart and perhaps eventually predict the behavior of this complex disease.

In summary, public health professionals view plague from two somewhat contradictory perspectives: From one viewpoint, plague must be known to clinicians as an uncommon disease of the West; the public may also benefit from awareness so that relatively simple preventive measures (dusting pet dogs and cats with flea powder and keeping away from sick or dead wild animals, especially rodents and rabbits) can be followed by residents of or visitors to rural areas of the West. In this context, the term Yersin's disease is apt. On the other hand, public health authorities must remain alert for plague pneumonia and, on a broader scale, they must monitor and study the potentially important new plague focus in the American West.

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Information

Physician Knowledge and Concerns About AIDS

ELIZABETH BARRETT-CONNOR, MD
La Jolla, California

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) has attracted an almost unprecedented amount of attention in the lay literature since it was first recognized in 1981. During a single week in 1982 more than 200 US newspapers carried articles about AIDS,[1] and a July 1983 *Newsweek* poll (*Newsweek*, August 8, 1983, pp 30-40) found that 91% of Americans had heard of AIDS. In contrast, the *Index Medicus* did not include this syndrome as a subject heading until the middle of 1983, and little attention has been paid to physician knowledge and concerns about AIDS. A mailed questionnaire was used to assess the knowledge and opinion of primary care physicians in San Diego County, California.

Methods

In October 1983 a 14-item questionnaire was mailed along with a stamped return envelope to all primary care physicians (257 in family and general practice, 198 in internal medicine and 104 in adolescent pediatrics) listed in the yellow pages of the 1983 San Diego telephone directory. Four questions requested responses about opinion and experience, and nine of ten true-false questions were based on statements of fact as published in two generally available review articles in the fall of 1983.[2,3] Responses were tabulated approximately eight weeks after the mailing.

(Barrett-Connor E: Physician knowledge and concerns about AIDS [Information]. West J Med 1984 Apr; 140:652-653)

From the Departments of Community and Family Medicine and Medicine, University of California, San Diego, School of Medicine.

Reprint requests to Elizabeth Barrett-Connor, MD, Department of Community and Family Medicine M-007, University of California, San Diego, School of Medicine, La Jolla, CA 92093.

Results

Of the 559 questionnaires mailed, 21 were returned by the postal service as undeliverable and an additional nine respondents indicated that they were not primary care physicians. The response rate for all others was 49% (260/529), of whom 104 were family physicians, 103 were internists and 53 were pediatricians.

Experimental and attitudinal responses by specialty are shown in Table 1. Only 3% of family practitioners or internists and no pediatricians reported great or moderate concern about acquiring AIDS from a patient; more than two thirds of all physicians reported no concern at all. There were 40% of family practitioners, 51% of internists and 65% of pediatricians who reported never or rarely treating gay patients. More than two thirds of all physicians thought that publicity about AIDS was excessive. Fewer than a third of pediatricians and fewer than half of family practitioners and internists reported interest in attending a seminar on AIDS.

As shown in Table 2, the percent of physicians making correct responses to factual statements did not differ significantly by physician specialty. Nearly 100% in each group knew that AIDS is most common in homosexual men, drug users, Haitians and hemophiliacs, 92% knew that a gay man with *Pneumocystis carinii* pneumonia probably has AIDS and 87% to 88% knew that AIDS is characterized by multiple opportunistic infections, has a poor prognosis and is not transmitted by casual contact. More than two thirds knew that Kaposi's sarcoma is not the most common presenting complaint and that health professionals are not at increased risk. Correct responses were less common for questions about the relative frequency of AIDS in California, the risk to children in the household of an AIDS patient and the early risk of AIDS in gay men with lymphadenopathy and altered T-cell function.

TABLE 1.—*Percent Responses to Experiential and Attitudinal Questions About AIDS From 260 Primary Care Physicians*

	Family Practice N=104 Percent	*Internal Medicine N=103 Percent*	*Pediatrics N=53 Percent*
Concern about acquiring AIDS from a patient			
Great to moderate	3	3	0
Slight	32	28	21
No concern	65	69	79
Frequency of treating gay patients			
Often	6	6	0
Sometimes	49	36	0
Rarely or never	40	51	65
Don't know	5	7	35
Believe publicity about AIDS is excessive	72	64	71
Would like to attend seminar on AIDS	48	45	29

TABLE 2.—*Percent Correct Responses to Factual Questions* About AIDS From 260 Primary Care Physicians*

Question	*Correct Answer*	*Family Practice Percent*	*Internal Medicine Percent*	*Pediatrics Percent*	*Total Percent*
The vast majority of cases occur in persons who are homosexual or bisexual men, IV-drug users, Haitian or hemophiliacs	True	98	99	100	99
A previously healthy gay man who develops *Pneumocystis* pneumonia has a high probability of having AIDS	True	89	92	98	92
The typical patient with AIDS has multiple opportunistic infections	True	90	87	83	88
Transmission of AIDS through casual contact has not been documented	True	82	94	90	88
The average life expectancy after the onset of classical AIDS is less than three years	True	84	90	87	87
The most common presenting finding of AIDS is Kaposi's sarcoma	False†	51	84	67	68
There are to date no proved cases of AIDS in health care professionals who have no other risk factors	True	64	73	58	66
AIDS is much more common in California than anywhere else in the United States	False‡	57	65	54	59
Children who are household contacts of patients with AIDS are at increased risk of developing AIDS	False§	55	60	46	55
At least half of gay men who have lymphadenopathy and altered T-cell function will develop classical AIDS within 12 months	False‖	22	38	19	27

*Questions are listed in order of percent correct responses, not in the order that they appeared on the questionnaire.
†The most common presenting illness is *Pneumocystis carinii* pneumonia.
‡There are twice as many cases reported from New York.
§Children who are household contacts have not yet been known to acquire AIDS.
‖AIDS has developed in less than a tenth.

Discussion

The present survey suggests that primary care physicians have a good level of knowledge about most of the important known facts of AIDS, including the population at risk, disease presentation and prognosis. Most are also aware of the limited potential for transmission by casual contact and are relatively unconcerned about acquiring the disease from their patients. They were least informed about the current geographic distribution of AIDS, about the low risk to children in households of AIDS patients and about the low immediate risk of AIDS in gay men presenting with lymphadenopathy as T-cell dysfunction. The last data are preliminary and the only information not included in either of the two review articles; this was the only information not known by at least 50% of physician respondents.

Because only 51% of physicians surveyed actually responded to the questionnaire, it is possible that nonrespondents are more or less knowledgeable about AIDS. However, both the response rate and responses were similar for family practitioners, internists and pediatricians, despite the fact that pediatricians reported rarely seeing gay patients and had lower levels of concern about contracting AIDS from patients.

Although these data show that the responding primary care physicians had a good level of factual knowledge about AIDS, they also suggest that most of them do not ascertain the sexual preferences of their patients. The frequency with which these physicians reported treating gay patients is much lower than the estimated 10% prevalence of male homosexuality.[4] Such a lack of awareness would limit their ability either to counsel gay patients about precautions designed to reduce the risk of AIDS or to suspect early AIDS on the basis of a patient's sexual practices.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

CURRENT PERSPECTIVES IN ALLERGY—Edited by E. J. Goetzl, MD, Professor of Medicine, Howard Hughes Medical Institute, Division of Allergy and Immunology, Department of Medicine, University of California, San Francisco, and A. B. Way, PhD, DSc, FRCP, Director and Professor, Department of Allergy and Clinical Immunology, Cardiothoracic Institute, London. Churchill Livingstone, 1560 Broadway, New York, NY 10036, 1982. 185 pages, $19.50 (softbound).

This slim volume contains 16 chapters writen by 18 well-regarded experts in a US-UK collaboration. The title is the first of a proposed series on "Contemporary Issues in Clinical Immunology and Allergy." Upcoming publications in this series are current perspectives in immunodermatology and immunology of respiratory diseases.

The format promotes rapid reading because of the liberal use of headings, short paragraphs and brief chapters. There are no reference citations in the body, but each chapter closes with reading selections. A number of helpful tables and diagrams are provided; there are fewer photographic reproductions and they are of poor quality at best.

As for content, the first third deals with introductory material and most of the rest with clinical categories. The goal of being current has largely been achieved. Some might argue that the dosage guides for theophylline on page 149, which were proposed originally in 1973, have now been supplanted. Newer evidence refutes the contention that a single bolus of steroids produces a physiologic response in asthma by two hours (p 162) and extends initial response time to four hours. The chapters on laboratory evaluation of allergy and on immunotherapy for specific prevention have a ring of originality that enhance their effectiveness. However, neither the laboratory evaluation chapter nor any other deals with the roles of bronchoprovocation or pulmonary function tests in evaluating the etiology and pathophysiology of asthma. The standard of accuracy is high and and rarely marred by a slipup such as the one in which kapok is listed as a synthetic substance (p 173) when it is a natural plant product.

The audience best served by this book are generalists not expert in allergy who require periodic updating on the subject. Allergy specialists will find litle new but will be interested in the views of eminent peers. High marks are earned by this volume for practicality, briefness and readability.

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Department of Medicine
University of California, Irvine
Orange

* * *

MANAGEMENT OF COMMON PROBLEMS IN OBSTETRICS AND GYNECOLOGY—Daniel R. Mishell, Jr, MD, Professor and Chairman, and Paul F. Brenner, MD, Associate Professor, Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles. Medical Economics Books, Oradell, NJ 07649, 1983. 531 pages, $27.50.

This book is a new departure—basically a standard-sized compendium of contemporary standard operating procedures from the present or recent faculty of the Womens Hospital of Los Angeles/University of Southern California Medical Center, the largest obstetric and gynecologic service in the United States. The book offers brief reviews covering the management and treatment of 116 obstetric or gynecologic problems. The material is often refreshingly clear and up-to-date, presented in a direct, straightforward manner. Timely references are included. One can consider many of the procedures as the current "American-way." The book is offered for reference but it provides an excellent review and update in obstetrics and gynecology.

The sequence of topics suggests a card file arbitrarily or even hastily assembled. The first chapters, "Drugs in Pregnancy" and "Management of the Incompetent Cervix," are followed by "Hydrocephalus." Then, after gynecologic, urologic and endocrine problems, the last chapter in the book is "Management of Fetal Demise." Subjects are often considered in one chapter on diagnosis, followed by a chapter on management. Topics are further broken-up; for example, there is a chapter on "Prepubertal Vulvovaginitis" but other vulvovaginidides are dealt with elsewhere. Why there is one chapter on urinary tract infection in pregnancy and later a consideration of this problem in nonpregnant women is speculative. For the "let's read the book through" enthusiast, all this may be very disconcerting.

There are excellent reviews of postdate pregnancy, fetal lung maturity, electronic fetal monitoring and even external version and placenta accreta. A fine section on oncology includes current cancer-screening, staging and treatment programs. Reproductive endocrinology and infertility are particularly well covered. Amenorrhea, hyperprolactinemia and androgen excess are dealt with clearly.

Omissions include potential side effects of glucocorticoid therapy for the stimulation of fetal pulmonary maturity, staging of endometriosis, sickle cell anemia in pregnancy and the beneficial effects of oral contraceptives. The discussion of abnormal labor, the incompetent cervix, sexually transmitted diseases and alleged sexual assault is inadequate.

Don't judge this valuable book by its cheap cover. Within, the criticisms are small considering the overall excellence of the reviews and protocols provided. Here is a storehouse of experience. Residents and progressive practitioners, especially, will welcome this book.

RALPH C. BENSON, MD
Professor and Chairman Emeritus
Department of Obstetrics and Gynecology
The Oregon Health Sciences University
Portland

* * *

A TEXTBOOK OF EPILEPSY—2nd EDITION—John Laidlaw, FRCP (Edin), Consultant Physician to Epilepsy Centre, Quarrier's Homes, Bridge of Weir, and Alan Richens, PhD, FRCP, Professor of Pharmacology and Materia Medica, Welsh National School of Medicine, Cardiff, Wales. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 544 pages, $59.00.

This is a multiauthored textbook dealing with the diagnosis and treatment of epilepsy. Many of the authors are well known authorities on the subject. The various chapters of the fairly comprehensive textbook are, in general, well written and the chapters are well referenced. The chapter on electroencephalography can, however, at best, be considered to be a brief introduction to the complex field.

The editors state that their intention was to offer a textbook on epilepsy so that those involved in different disciplines should be able to appreciate work being done by those in disciplines other than their own. This second edition of the textbook meets the editors' objectives.

This book is recommended for physicians who are not neurologists and who are interested in and take care of epileptic patients.

MASUD SEYAL, MD, PhD
Assistant Professor of Neurology
University of California, Davis, Medical Center
Sacramento

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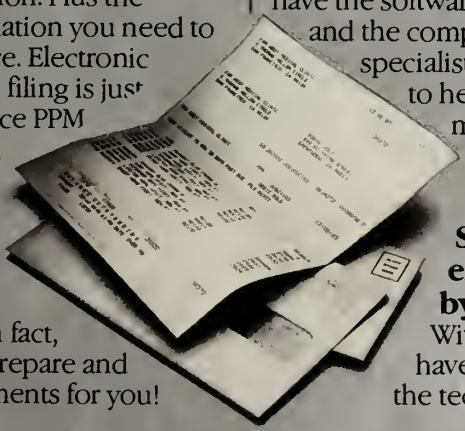

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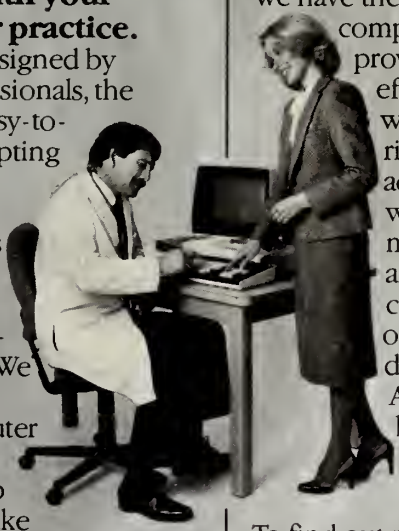

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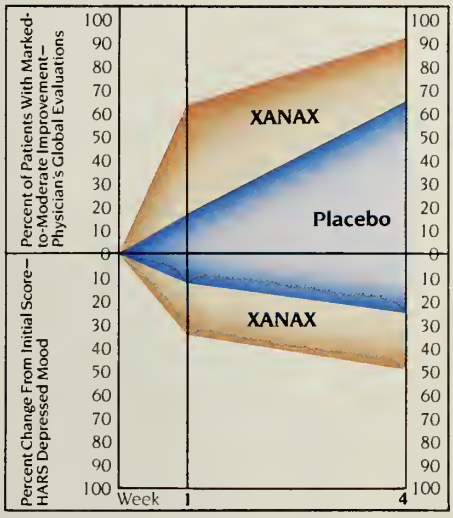

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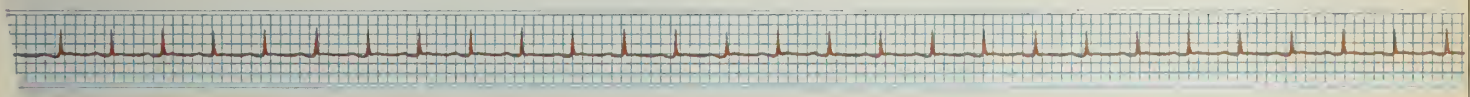

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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. BS-1

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(Continued from Page 563)

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 26-28—**Psychology of Health and Illness: Mind-Body Relationships.** Albuquerque. Thursday-Saturday. Marriott Hotel. 10 hrs. AMA Cat. I, NM Cat. IV. Contact: Office of CME, UNM School of Medicine, Albuquerque 87141. (505) 277-3942.

May 3-4—**New Mexico Medical Society Annual Meeting.** Santa Fe. Thursday-Friday. Hilton Inn. 10 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Ste 204, Albuquerque 87108. (505) 266-7868.

May 5—**Anesthesia Update 1984.** Albuquerque. Saturday. Savage Auditorium, Presbyterian Medical Center. 6 hrs. AMA Cat. I, NM Cat. IV. Contact: Jacob Maincer, Jr, MD, 1820 Randolph SE, Albuquerque 87106. (505) 247-9749.

May 10-12—**Arrhythmia Diagnosis and Management for the Primary Care and Emergency Physician.** Albuquerque. Thursday-Saturday. Presbyterian Medical Center. 18 hrs. AMA Cat. I, NM Cat. IV. Contact: Barry W. Ramo, MD, 201 Cedar SE, #604, Albuquerque 87106. (505) 242-2796.

May 18-19—**Breast Cancer: Current Concepts and Controversies.** Albuquerque. Friday-Saturday. Clarion Four Seasons Hotel. 10 hrs. AMA Cat. I, NM Cat. IV. Contact: Office of CME, UNM School of Medicine, Albuquerque 87141. (505) 277-3942.

May 24-25—**Chronic Pain: Current Status and Future Directions.** Santa Fe. Thursday-Friday. La Fonda Hotel. 10¼ hrs. NM Cat. IV. Contact: Ms Helene Slansky, Coordinator, Santa Fe Neurological Sciences Institute, St. Vincent Hospital, Box 5764, Santa Fe 87501. (505) 983-4744.

June 8-9—**New Mexico Chapter, American College of Surgeons.** Las Cruces. Friday-Saturday. Holiday Inn. Contact: Robert H. Wilbee, MD, 2435 Telshor Blvd., Las Cruces 88001.

July 16-19—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, P.O. Box 23070, Albuquerque 87192. (505) 298-5300.

(Continued on Page 660)

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(Continued from Page 658)

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

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Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contac: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South. Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

EMERGENCY MEDICINE

June 7-8—**Poisoning and Toxicologic Emergencies.** Portland. Thursday-Friday. Marriott Hotel. Contact: OHSU-CME.

June 13-15—**Oregon Chapter, American Trauma Society.** Portland. Wednesday-Friday. Sheraton-Airport. Contact: OHSU-CME.

November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

MEDICINE

June 11-15—**American College of Physicians MKSAP Program.** Portland. Monday-Friday. Marriott Hotel. Contact: Postgraduate Dept., ACP, 4200 Pine Street, Philadelphia, PA 19104.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

PERINATAL MEDICINE

June 22-24—**Symposium on Perinatal Medicine.** Portland. Friday-Sunday. Thunderbird-Jantzen Beach. Contact: OHSU-CME.

SURGERY

December 7-8—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

May 11—**Infectious Diseases in Clinical Practice.** Portland. Friday. OHSU Campus. Contact: OHSU-CME.

(Continued on Page 662)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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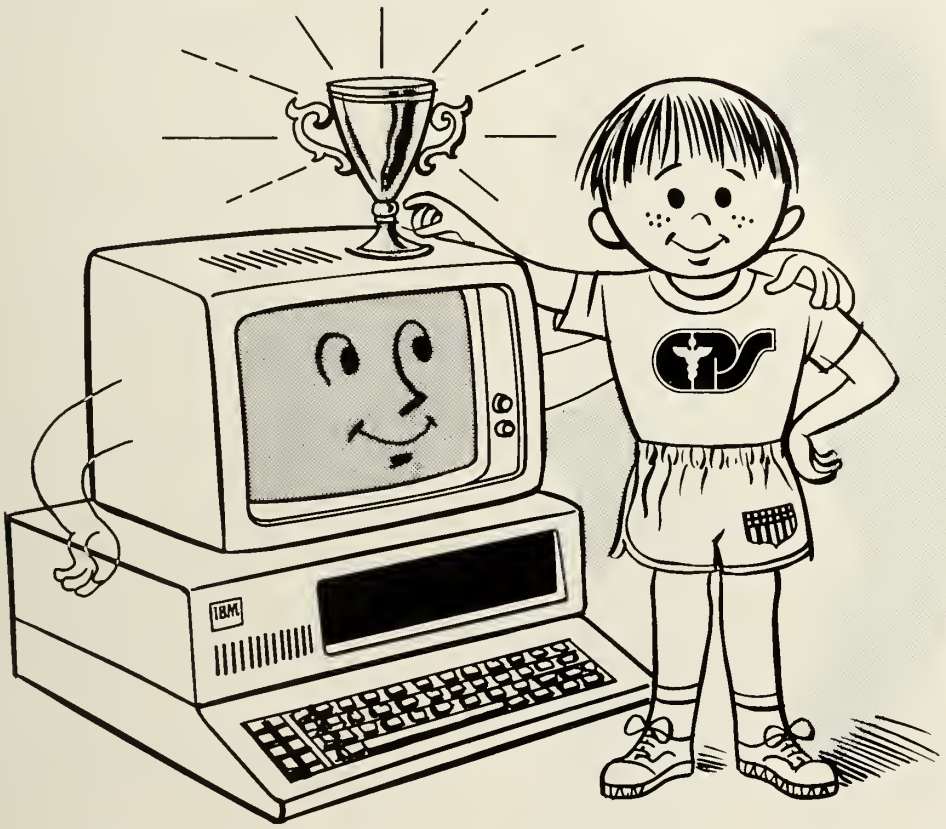

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(Continued from Page 660)

June 1-2—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

June 22-23—**Exercise and Fitness.** Portland. Friday-Saturday. Red Lion-Lincoln Street. Contact: OHSU-CME.

September 7-8—**The Ashland Conference: Immunology and Allergy in Primary Care.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE GRAND ROUNDS

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Wednesday—8:00-9:00 a.m. Contact: Thomas Schwenk, MD, (801) 581-8633.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo. UT 84601. (801) 373-7850 (Ext 2143).

* * * *

April 20—**Symposia in Infectious Disease** (Sponsor: University of Utah). Friday. Salt Lake City, Hotel Utah. Credit and fee to be announced. Contact: Zell McGee, MD, (801) 581-8201.

(Continued on Page 667)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fitfh West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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Announcing a major advance in cardiovascular therapy

CARDIZEM™ (diltiazem HCl)

30 mg and 60 mg tablets

CALCIUM CHANNEL BLOCKADE

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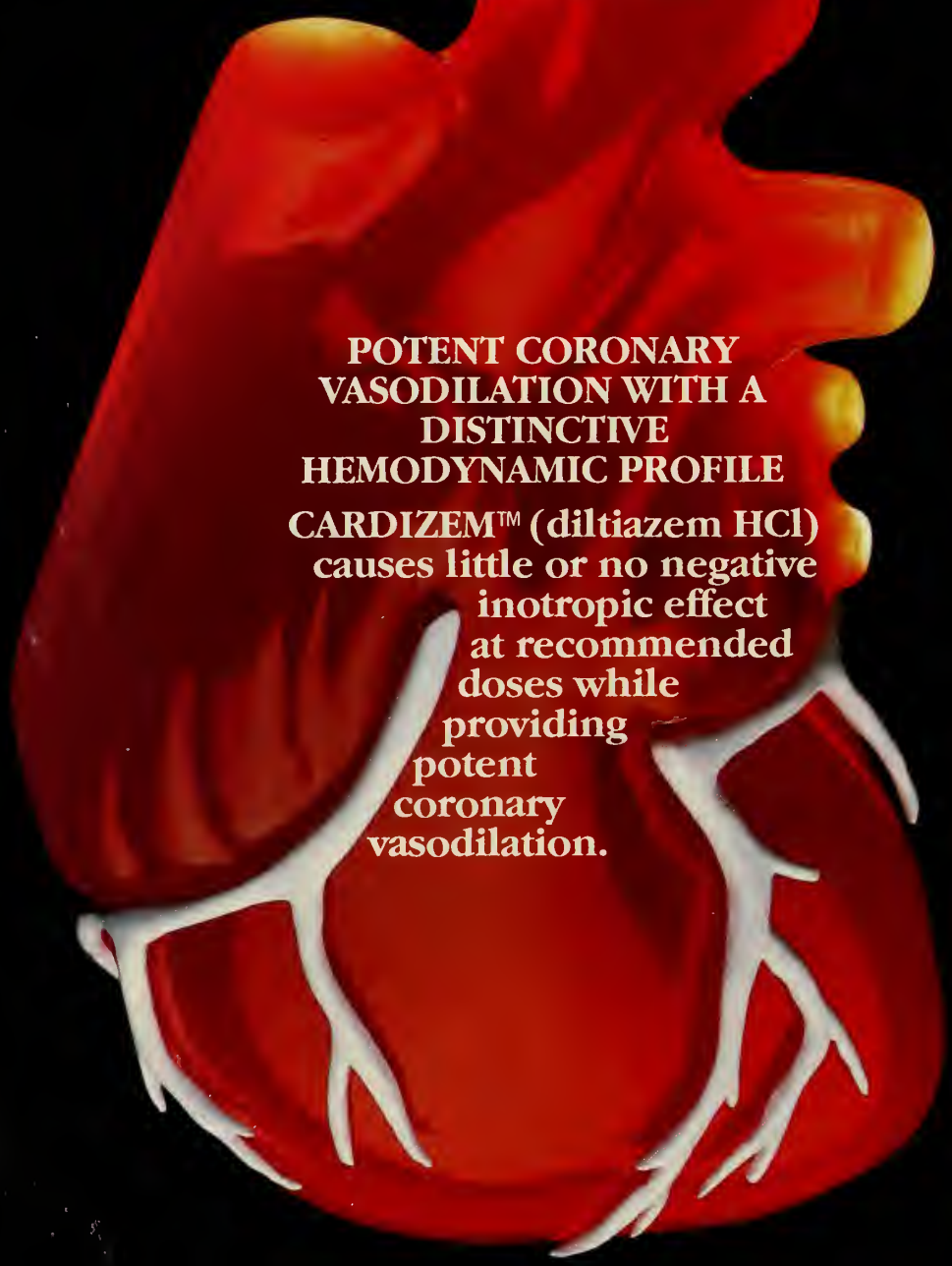

POTENT CORONARY VASODILATION WITH A DISTINCTIVE HEMODYNAMIC PROFILE

CARDIZEM™ (diltiazem HCl) causes little or no negative inotropic effect at recommended doses while providing potent coronary vasodilation.

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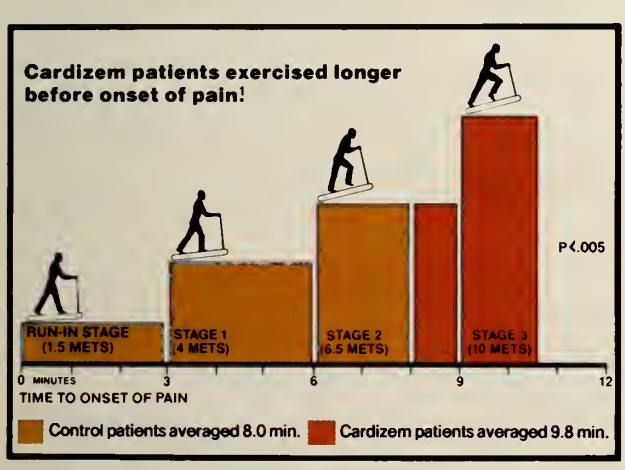
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY* WITH A LOW INCIDENCE OF SIDE EFFECTS

Calcium channel blockade with CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

CARDIZEM™ (diltiazem HCl) ALLOWS PATIENTS TO SIGNIFICANTLY PROLONG EXERCISE TOLERANCE, EVEN IN DEMANDING BRUCE PROTOCOL EXERCISE TESTS[1] (n = 15)†



This study is of special significance because patients not only exercised longer but *to the next higher stage* in the Bruce protocol.

A Bruce protocol with a run-in stage was used for all tests. Each stage lasts three minutes.

In other studies, Cardizem produced 41% to 68% reduction of Prinzmetal's variant angina attacks[2]

†This study is a report from one center in a multicenter study.

Therapy with Cardizem produced a low incidence of side effects.

In placebo-controlled trials (222 patients) conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with Cardizem in 959 patients in controlled and uncontrolled U.S. trials have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

Other reactions reported infrequently (less than 1%) are listed in full prescribing information on adjacent page.

Please see adjacent page for full prescribing information.

References:

1. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl): 234-238, 1980.
2. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.

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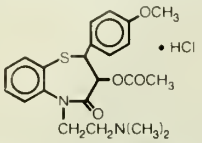
PROFESSIONAL USE INFORMATION

DESCRIPTION

CAROIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-8enzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Oiltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CAROIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CAROIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CAROIZEM is believed to act in the following ways:

1. Angina Oue to Coronary Artery Spasm: CAROIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CAROIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Oiltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CAROIZEM in doses of up to 240 mg/day nas resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Oiltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CAROIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CAROIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CAROIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Oesacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INOICATIONS ANO USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CAROIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CAROIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINOICATIONS

CAROIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CAROIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (four of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CAROIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CAROIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem tid of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to the drug is uncertain.

PRECAUTIONS

General. CAROIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CAROIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CAROIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CAROIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CAROIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. 8ecause many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CAROIZEM therapy was not greater than that reported during placebo therapy

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CAROIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Oermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CAROIZEM.

Experience in 959 patients taking oral doses of CAROIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LOH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

8radycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-degree AV 8lock	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LO_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LO_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE ANO AOMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Oue to Coronary Artery Spasm. Oosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CAROIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CAROIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NOC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NOC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

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3/83

(Continued from Page 662)

April 26-28—**35th Western Institute on Epilepsy** (Sponsor: University of Utah). Thursday-Saturday. Hotel Utah, Salt Lake City. Credit and fee to be announced. Contact: Claire Turner, (801) 581-5809.

May 10-11—**Ethics and Health; Cost of Treatment/Dilemmas in Allocation** (Sponsor: University of Utah). Thursday-Friday. Credit and fee to be announced. Contact: Claire Turner, (801) 581-5809.

May 16—**Day in Nephrology at the University of Utah** (Sponsor: University of Utah). Wednesday. University Medical Center. 6 hrs. $30.00. Contact: Rosalie Lammle, (801) 581-8664.

June 3-6—**American Society for Lasers in Medicine and Surgery** (Sponsor: University of Utah). Monday-Wednesday. Salt Lake City. 8 hrs. Fee to be announced. Contact: John Dixon, MD, (801) 581-8201.

June 8-9—**Advanced Trauma Life Support (ATLS)** (Sponsor: University of Utah/Utah State Health Department). Friday-Saturday. Salt Lake Hilton Hotel. 14.5 hrs. $350. Contact: Kim Tanner, (801) 561-4594.

June 18-21—**School on Alcoholism and Other Drug Dependencies** (Sponsor: University of Utah). Monday-Thursday. University Medical Center. 26 hrs. $300. Contact: James Swenson, MD, (801) 581-7985.

July 15-20—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, Wyoming. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art** (Sponsor: University of Utah). Wednesday. Jackson Lake Lodge, Wyoming. 22 hrs. Fee to be announced. Contact: John D. Armstrong, MD, (801) 581-7553.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

April 26—**Travel and Medicine.** Seattle. Thursday. Park Hilton Hotel. Contact: U/W.

April 27-28—**Industrial Back Pain.** Seattle. Friday-Saturday. Contact: U/W.

April 28—**Medicine and Religion.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

May 3-5—**Primary Care Update.** Thursday-Saturday. Cavanaugh's Motor Inn, Tri-cities. Contact: Linda Koch, Washington Academy of Physician Assistants, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 623-4801.

May 9—**Ophthalmology.** Seattle. Wednesday. 4:00-9:00 pm, Gould Auditorium. 4 hrs. Cat. I. $25. Contact: Charlotte Kennedy, Northwest Hospital, 1550 N. 115th, Seattle 98133. (206) 364-0500, Ext. 1737.

May 10—**Health Issues for Exercising Women.** Seattle. Thursday. Westin Hotel. Contact: U/W.

May 11—**Dermatology.** Seattle. Friday. 4:00-9:00 pm. Gould Auditorium. 4 hrs. Cat. I. $25. Contact: Charlotte Kennedy, Northwest Hospital, 1550 N. 115th, Seattle 98133. (206) 364-0500, Ext. 1737.

May 11—**Adverse Drug Reactions in Surgery.** Seattle. Friday. Ballard Hospital. Contact: U/W.

May 16-18—**Noise Measurement and Control.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

May 18—**Basic Computer Understanding.** Seattle. Friday. Seattle Trade Center. Contact: U/W.

May 24-25—**Hereditary Diseases of the Nervous System.** Seattle. Thursday-Friday. Mayflower Park Plaza. Contact: U/W.

June 1-2—**Health Hazards in the Modern Office.** Seattle. Friday-Saturday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

June 1-2—**Prenatal Diagnosis for the 80's.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: U/W.

June 1-2—**1st Mental Health Public Policy Forum.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

June 2—**Making Senate Bill 3645 Work.** Seattle. Saturday. Westin Hotel. Contact: U/W.

June 2—**Eye Care for the Primary Physician.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

June 8-9—**Fifth Annual Western Washington Cancer Conference.** Rosario Resort, San Juan Islands. Friday-Saturday. 9 hrs. Cat. I. $80. Contact: Annie M. Sakaguchi, Program Director, American Cancer Society, PO Box C-19140, Seattle 98109-1140. (206) 283-1152.

June 8-9—**Cardiology and Nephrology.** Seattle. Friday-Saturday. Museum of History and Industry. Contact: U/W.

(Continued on Page 674)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

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CALIFORNIA—URGENT CARE. Positions available for Spring 1984 in free-standing, urgent care settings in several locations. Board certication or eligibility in Emergency Medicine, Family Practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Avenue, Suite 500, Oakland, CA 94610, (415) 832-6400.

PEDIATRICIAN BC/BE to join three young progressive pediatricians in growing area of Salt Lake City. Superb access to outdoor activities. New hospital facilities adjacent. Contact Chuck Norlin, MD, 3449 South 4155 West, West Valley City, UT 84120.

MINOR EMERGENCY CLINIC: Full-time physician opening for the Sacramento area. One year contract minimum. Malpractice coverage provided. Dr Kendall Bauer, 815 Mast Ct, Folsom, CA 95630; (916) 933-1449 evenings.

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PEDIATRICIAN—Solo practice in Southeastern New Mexico. Ideal family living in prosperous community serving 85,000. Income guarantee, new office available adjacent to 106-bed JCAH-accredited hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

BEAUTIFUL WASHINGTON STATE—One General Internist sought to join another Internist in an HMO with 15 well-trained Board-certified Family Practitioners in Spokane, Washington. An unusual opportunity to serve as a full-time in house consultant in an organization where continuity of care, patient education/preventive medicine, and high quality personal-style care are emphasized. Prefer interest/training in medical Oncology or Geriatrics. Excellent salary and benefits. Spokane is a delightful city containing an exceptionally fine medical community and superb, year-round outdoor recreation. Affiliated with Group Health Cooperative of Puget Sound. For further information contact: Carl Baum, MD, Group Health of Spokane, N. 3919 Maple Street, Spokane, WA 99205; (509) 326-6900.

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GENERAL INTERNAL MEDICINE SPECIALIST position open with 37-member multi-specialty group. Excellent practice opportunity; full range of benefits; early shareholder status; all practice costs paid. Prefer recent residency trained physicians. For more information contact: Daniel Small, MD, Medical Director, or David Graham, Asst Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

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GENERAL PRACTITIONER—to join busy 12 physician office in beautiful Napa Valley. Must be skilled in minor surgery, office orthopedics and capable of inpatient and outpatient care of general medical problems. Contact: Ernest Arras, MD, Permanente Medical Group, 3284 Jefferson Street, Napa, CA 94558; (707) 255-3942.

GENERAL INTERNIST, Board certified/eligible: Multi-specialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact A. J. Grose, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

(Continued on Page 670)

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(Continued from Page 668)

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POSITION OPEN: Medical Ophthalmologist wanted in large midwest practice that is affiliated with university training program. Excellent medical skills required. Knowledge of Argon Laser preferable. Opportunity to assist in surgery and learn Yag Laser available. Salary $75,000 plus generous benefits and rapid advancement depending on qualifications. Send résumé to: Box 6379, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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PRIMARY CARE PHYSICIAN—(General Practitioner or General Internist) for employment by the State of California at San Quentin Prison Hospital. Civil service status. Forty hours per week. Beginning salary $42,792-$61,464 depending on qualifications and experience. For further information contact: Jack J. Williams, MD, at (415) 454-1460.

NEUROSURGEON—Southeastern New Mexico. To establish new practice in growing community serving 85,000. New 106-bed hospital, JCAH-accredited. Has newly operational CAT. Income guarantee. New office available adjacent to hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

BOARD CERTIFIED Oncologist, Cardiologist, Internist, Neurosurgeon, Otorhinolaryngologist for Southeastern Washington—Tri-Cities, 150,000 population. Outdoor activities abound. Group or solo opportunities. Contact Vesta Skiens, Kennewick General Hospital (509) 586-6111 (309).

BOARD CERTIFIED GENERAL INTERNIST to join same in growing private practice in Central California. City of 115,000, one and a half hours from San Francisco; Sacramento; five and a half hours from Los Angeles. Excellent opportunity. Contact Barbara Mandell, MD, 1700 McHenry Village Way, Modesto, CA 95350.

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LOS ANGELES AREA—GENERAL INTERNIST FOR PRIVATE PRACTICE. Practicing Board certified IM seeks associate. Prefer University trained. Send CV to Suite 170, 2800 Veterans Boulevard, Matairie, LA 70002.

EMERGENCY PHYSICIAN—Full-time only to join progressive partnership practicing only Emergency Medicine. Must be Emergency Board eligible or certified and willing to locate in Sacramento area. Send CV to M. Dorso, S.E.M.G., P.O. Box 214584, Sacramento, CA 95821.

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INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PG II AND III INTERNAL MEDICINE POSITIONS (Must be graduates from school accredited by the AAMC.) Available July 1984 at the University of Nevada School of Medicine in Reno. Excellent faculty and program with a heavy commitment to teaching and a strong emphasis in training of general internists. Elective rotations in all subspecialty areas available. Combined Dean's VA Hospital and county-private hospital experience. Outstanding location at the base of the Sierras, 30 miles from Lake Tahoe. Contact Stephen Hall, MD, (702) 786-7200, ext. 452, or write 1000 Locust St., Reno, NV 89502. EOE/AA

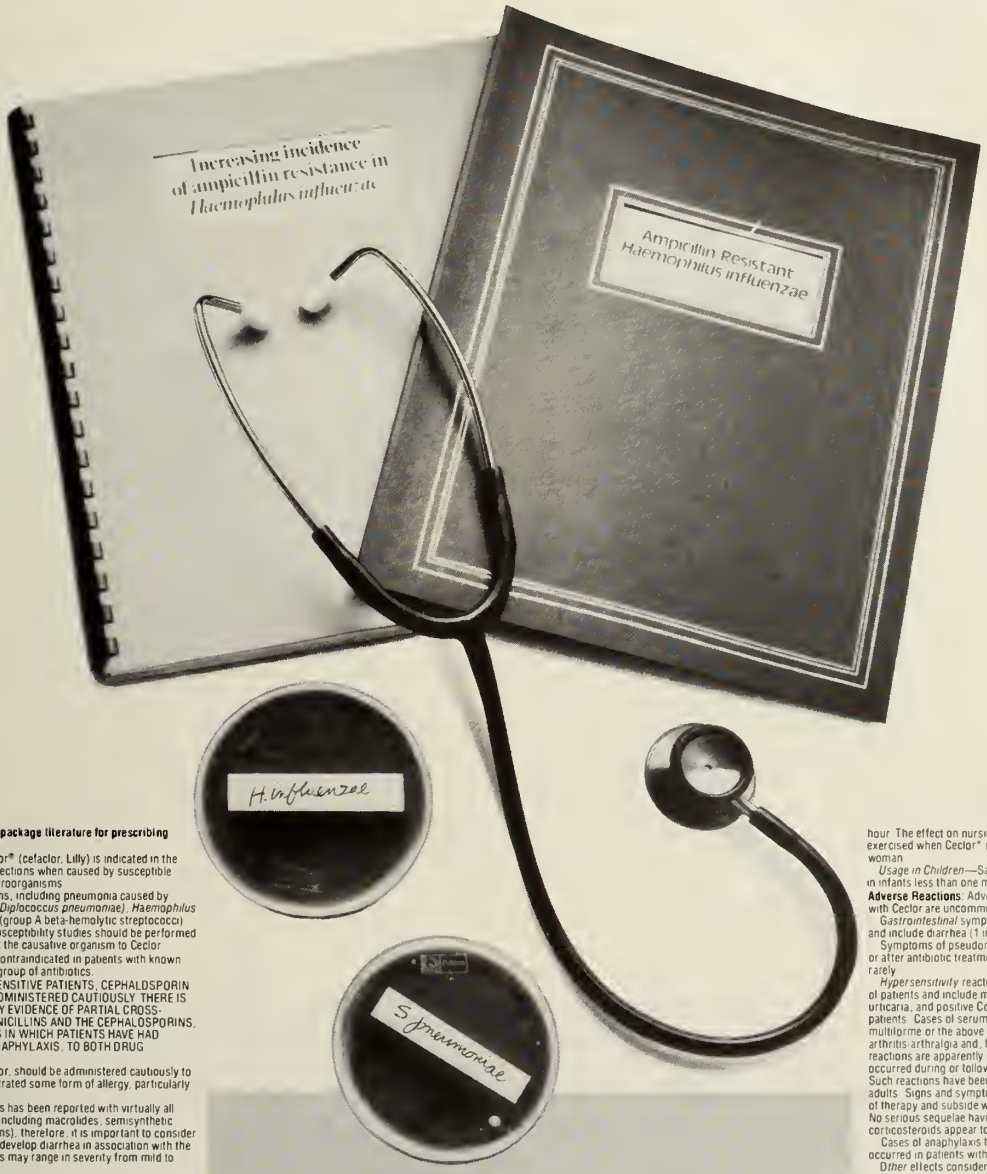
PRIMARY CARE PHYSICIAN wanted to share office of podiatrist with established Sports Medicine practice in Irvine. Anticipate rapid growth of athletic patient load. Interest in Sports Medicine, runner preferred. New office building—ready June 1984. (714) 752-0044.

GP/FP FOR NEW MEXICO rural town. 100+ bed hospital. Specialists. Office practice, gross 130K, young, trained staff, equipment, low entry cost for full partner; may sell-out totally in 6-12 months. Reply Box 6422, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

GENERAL PRACTITIONERS—Specialists—Full-time positions or Locum Tenens. If you're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

(Continued on Page 676)

An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGDT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.*

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*:91, 1975.
2. Antimicrob. Agents Chemother., *11*:470, 1977.
3. Antimicrob. Agents Chemother., *13*:584, 1978.
4. Antimicrob. Agents Chemother., *12*:490, 1977.
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II 880. Washington, D.C.: American Society for Microbiology, 1978.
6. Antimicrob. Agents Chemother., *13*:861, 1978.
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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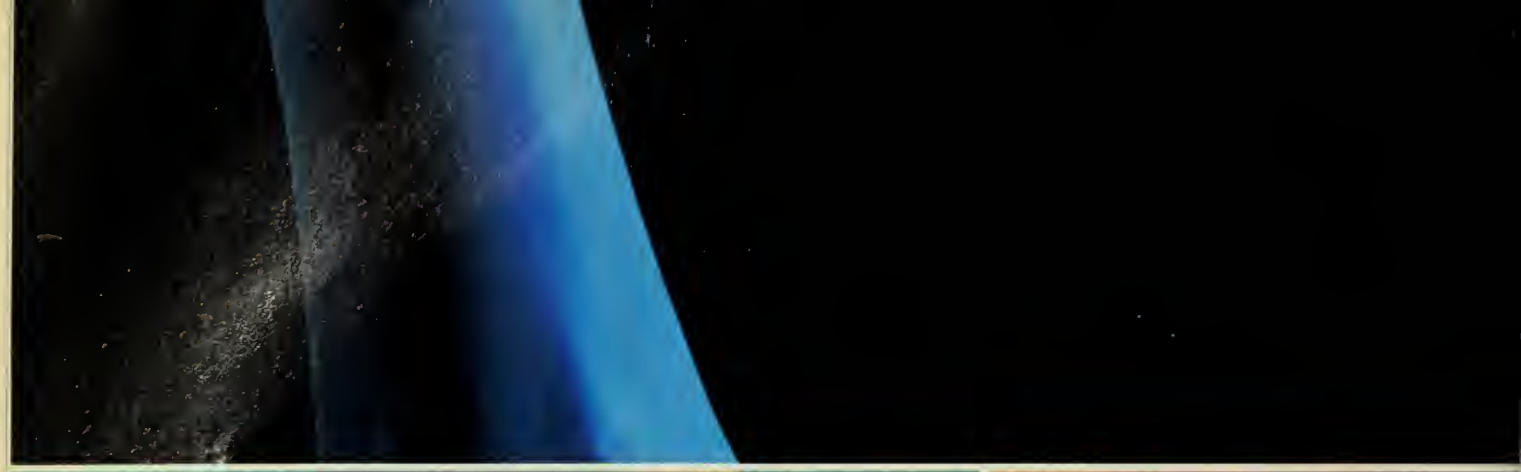

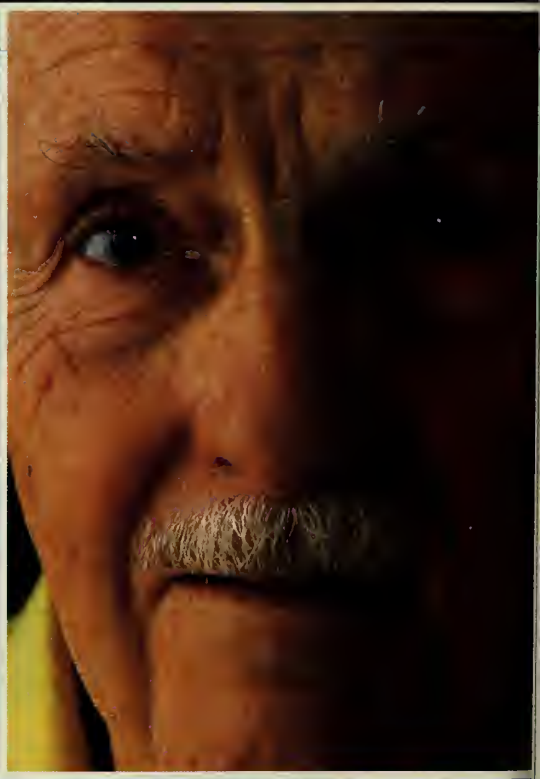

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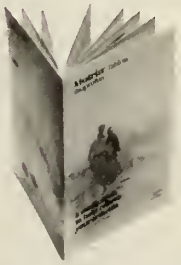
Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.



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(ibuprofen)

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Motrin® Tablets (ibuprofen)
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.
Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.
Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.
The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.
Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.
Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.
Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.
Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness;* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence less than 1%—Probable Causal Relationship*
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence less than 1%—Causal Relationship Unknown*
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.
*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
Caution: Federal law prohibits dispensing without prescription.

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MED B-7-S

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(Continued from Page 667)

June 9—**Radiology Northwest.** Seattle. Saturday. U/W CDMRC. Contact: U/W.

June 14-15—**Use of Microcomputers in Occupational Safety and Health.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

June 15-16—**CT Scanning in Radiation Therapy.** Seattle. Friday-Saturday. Sheraton. Contact: U/W.

June 15-17—**Nutrition Update for Clinical Dieticians.** Union. Friday-Sunday. Alderbrook Inn. Contact: U/W.

June 18-22—**Trauma: The First 3 Hours.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W.

June 21-22—**Stroke: Current Concept.** Seattle. Thursday-Friday. 8:30 am-5:00 pm. Gould Auditorium. $150, physicians; $75, others. 12 hrs. Cat. I. Contact: Charlotte Kennedy, Northwest Hospital, 1550 N. 115th, Seattle 98133. (206) 364-0500, Ext. 1737.

June 23-27—(IDAHO) **Ethics at the Edges of Life.** Sun Valley. Saturday-Wednesday. Elkhorn. Contact: U/W.

July 4-10—(OREGON) **Medicine and Civilization.** Bend. Wednesday-Tuesday. Inn at the 7th Mountain. Contact: U/W.

July 10-13—(OREGON) **Medicine in Shakespeare's Time.** Ashland. Tuesday-Friday. Contact: U/W.

July 12-13—**Second Annual Conference on Occupational Hazards to Health Care Workers.** Seattle. Thursday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 22-26—**Annual Summer Meeting 1984. Washington State Academy of Ophthalmology.** Orcas Island. Sunday-Thursday. Rosario Resort. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

July 27-29—**Seafair VI Pediatric Anesthesia and Intensive Care.** Seattle. Friday-Sunday. Seattle Sheraton. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave, Suite 900, Seattle 98121. (206) 623-4801.

August 29-September 4—(ALBERTA) **Scientific Aspects of the Art of Dance.** Banff Centre, Banff, Alberta. Contact: U/W.

WYOMING

June 24-28—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Thursday. Contact: WMS, P.O. Drawer 4009, Cheyenne 82003-4009. (307) 634-2424.

July 15-20—**Summer Update in Clinical Microbiology and Immunology.** University of Utah at Jackson Hole. Sunday-Friday. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art.** University of Utah at Jackson Lake Lodge. Wednesday. 22 hrs. Contact: John D. Armstrong, MD, (801) 581-7553.

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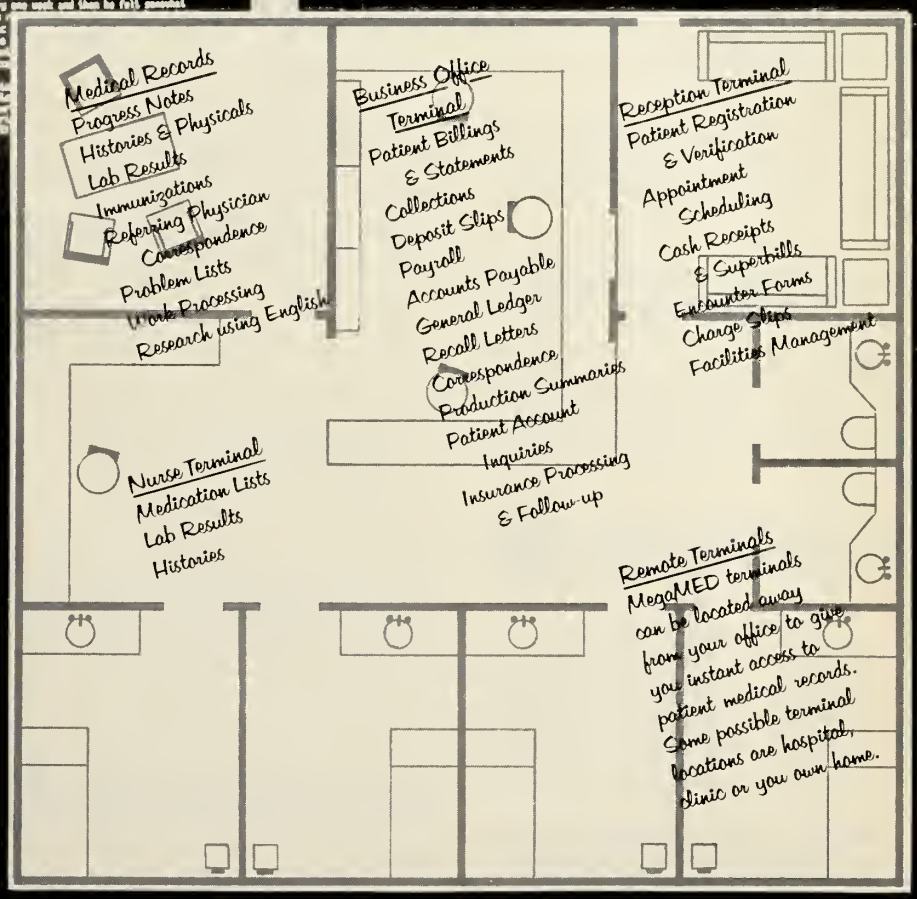

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(Continued from Page 670)

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Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: June 8-12, 1984, Valdez Convention Center.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 27-28, 1984, Scottsdale Conference Center, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and Country, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 20-22, 1984, Mark Marriott, Vail.

Hawaii Medical Association—320 Ward Ave., Suite 200. Honolulu 96814. (808) 536-7702. Annual Meeting: November 9-11, 1984, Kauai Surf Hotel, Kauai.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-28, 1984, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane. Reno 89502. (702) 825-6788. Annual Meeting: May 3-6, 1984, Desert Inn, Las Vegas.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 2-4, 1984, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: April 27-29, 1984, Salizhan Lodge, Gleneden Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 24-28, 1984, Jackson Lake Lodge, Moran.

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Improving the outlook... in mixed depression and anxiety

A rational approach, combining

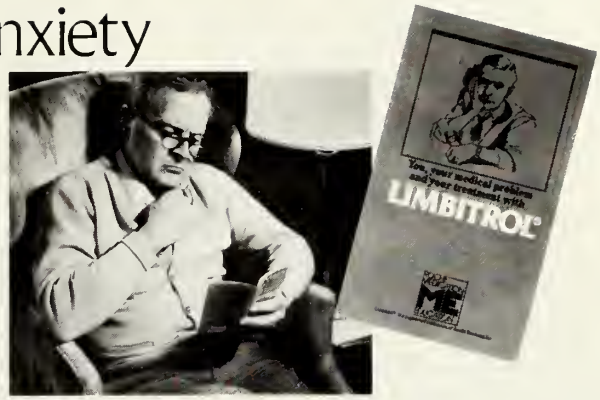
- The standard antidepressant: amitriptyline
- The proven anxiolytic: Librium® (chlordiazepoxide HCl/Roche) Ⓥ

Marked improvement often occurs as early as the first week.

Headache, insomnia or GI upsets associated with mixed depression and anxiety often respond quickly.

Feeling better, patients feel encouraged to stay the course—therefore, fewer dropouts due to side effects: $p < 0.006$ compared to amitriptyline.* Patients should be cautioned about the combined effects of Limbitrol with alcohol and other CNS depressants, and about activities requiring complete mental alertness such as operating machinery or driving a car.

*Feighner JP: *Psychopharmacology* 61:217-225, Mar 22, 1979.



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Because an informed patient is more responsive...

This easy-to-read brochure explains the rationale of dual therapy with Limbitrol and encourages patient compliance. To obtain a complimentary supply, please contact your Roche representative.

In moderate depression and anxiety

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Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

LIMBITROL® Tablets Ⓥ
Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose* packages of 100, Prescription Paks of 50.

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Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
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Rapid clearing through dual action

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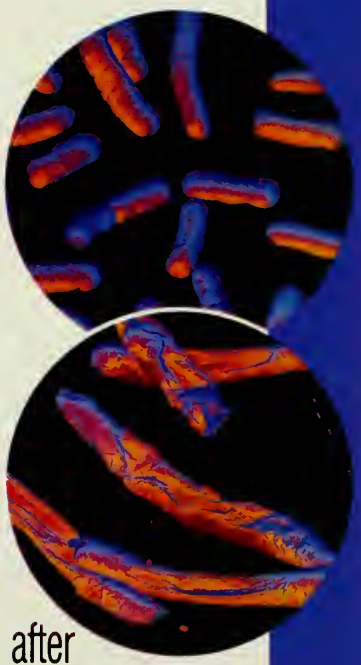
Strong on results.

before

Color-enhanced scanning electron micrograph shows *E. coli* 736 culture growing on Adams and Roe agar.



after

E. coli 736 culture after 24-hour incubation with Bactrim (trimethoprim and sulfamethoxazole/Roche) at 5×MIC. Note distorted shape of destroyed bacteria.

Simple to take.

ROCHE®

In recurrent urinary tract infections

- **Clears the urinary tract of a wide range of susceptible pathogens**
- **Rapidly relieves symptoms of urgency and dysuria**
- **Destroys potential pathogens that colonize the vaginal area**

Bactericidal against *E. coli* and other uropathogens *in vitro*

Bactrim demonstrates bactericidal action against major uropathogens *in vitro*. *E. coli, Klebsiella pneumoniae* and *Enterobacter* were all rapidly destroyed by Bactrim at 5× MIC levels—and these levels are usually greatly exceeded in the urine after a standard dosage of Bactrim DS.[1] However, *in vitro* activity does not necessarily correlate with clinical results.

Unsurpassed efficacy in clinical practice

In chronic or recurrent urinary tract infections, Bactrim is highly effective[2] and has been repeatedly recommended for its strong results,[3] its site-to-source action (in urinary tract, vagina and bowel)[4] and its ability to penetrate the renal parenchyma in chronic pyelonephritis.[5] Clinicians often prefer Bactrim as treatment for the entire course of therapy when the organism is known to be susceptible,[6] and as first-line therapy in recurrent urinary tract infections.[7]

Effective and economical *b.i.d.* therapy

Just one Bactrim DS tablet *b.i.d.* for 10 to 14 days provides effective, economical therapy for recurrent urinary tract infections.

Bactrim is indicated for the treatment of recurrent urinary tract infections due to susceptible strains of *E. coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris* and *Proteus morganii*. However, it is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single antimicrobial agent rather than the combination.

Maintain adequate fluid intake during therapy. Bactrim is contraindicated in pregnancy at term, during lactation, in infants under two months of age and in documented megaloblastic anemia due to folate deficiency.

Bactrim™ DS

(trimethoprim and sulfamethoxazole/Roche)

B.I.D. for enhanced compliance.

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Please see summary of product information on the following page.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Wormser GP, Keusch GT, Heel RC: *Drugs 24*:459-518, Dec 1982. 3. Ronald AR: *Clin Ther 3*:176-189, 1980. 4. Rubin RH, Swartz MN: *N Engl J Med 303*:426-432, Aug 21, 1980. 5. Cunha BA: *Postgrad Med 70*(6):149-156, Dec 1981. 6. Neu HC: *Infectious Diseases 10*(6):4, 19, Jun 1980. 7. Jones SR: *Ration Drug Ther 13*(11): 1-5, Nov 1979

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:
Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.
For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.
For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.
For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.
Also for the treatment of documented *Pneumocystis carinii* pneumonitis.
Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.
Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.
Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.
Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.
Dosage: Not recommended for infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:
Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.
Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.
For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:
Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.
PNEUMOCYSTIS CARINII PNEUMONITIS:
Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.
Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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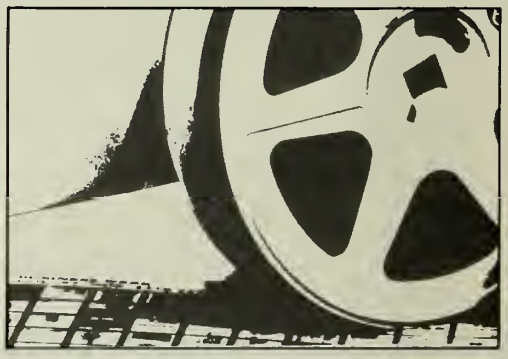

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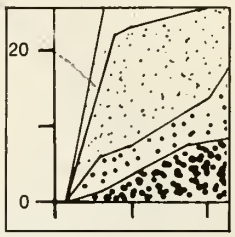

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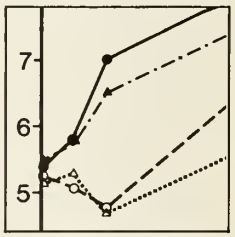

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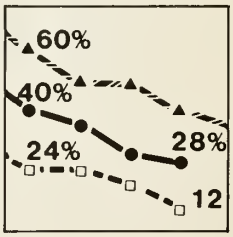

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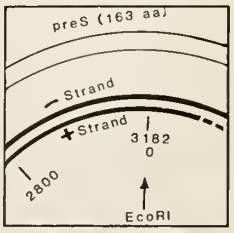

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CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.
Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.
Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.
Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.
PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).
Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.
Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.
Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.
Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.
Pediatric Use — Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.
Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.
Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.
OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.
Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.
Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)
Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.
DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.
For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).
For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).
Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.
For full prescribing information, consult package insert.
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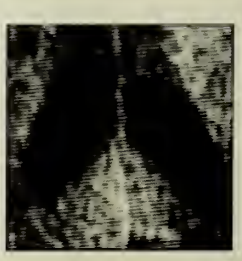

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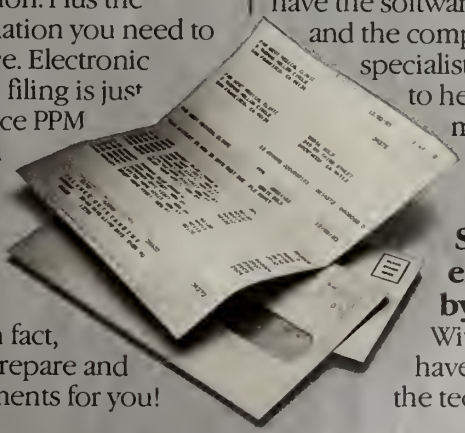

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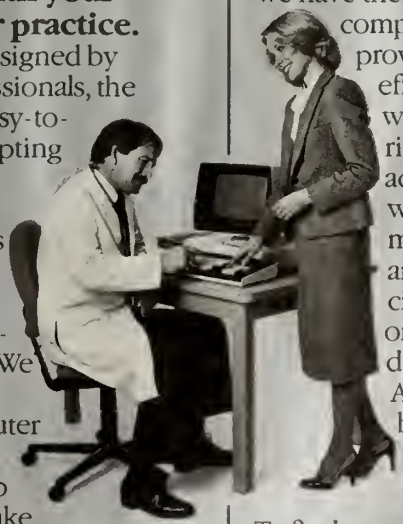

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The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

■ = objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

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Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

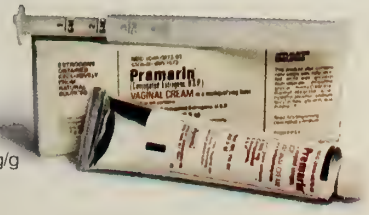
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

FOR ATROPHIC VAGINITIS

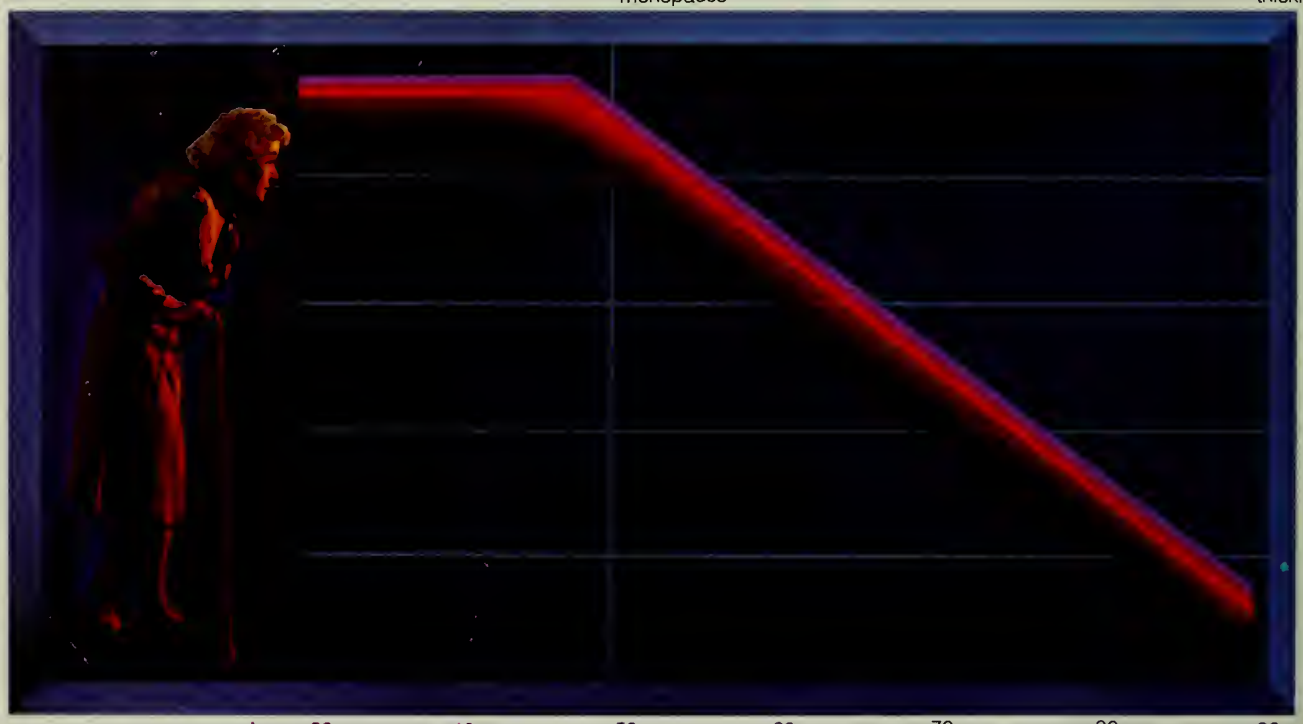
PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/g

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis.

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).
WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.
PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.
ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment, increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight, reduced carbohydrate tolerance; aggravation of porphyria, edema; changes in libido.
ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.
DOSAGE AND ADMINISTRATION:
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (*e.g.*, three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.
Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.
Osteoporosis (to retard progression)—1.25 mg daily, cyclically.
3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (*e.g.*, three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.
HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **8934/584**

Ayerst®
AYERST LABORATORIES
New York, N.Y. 10017

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Dr Mann has served as president of the Santa Fe County Medical Society and State Epidemiologist, State of New Mexico Health and Environment Department, Santa Fe. He now is on assignment for the Centers for Disease Control.

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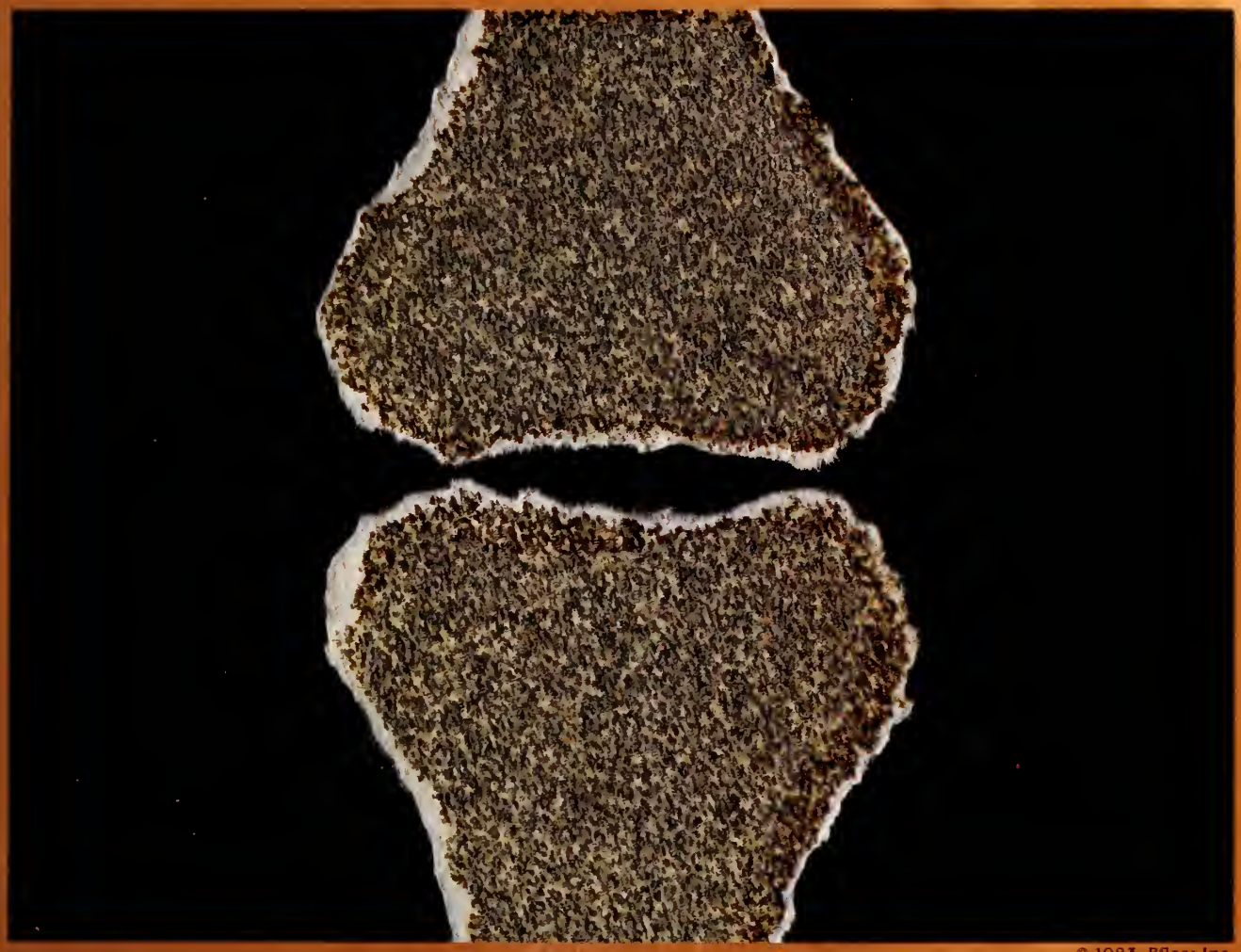
★ **Affiliated Clinical Investigation Societies: The Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**



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This is how an arthritis patient's joints often feel.

You can help these patients feel better with one-a-day FELDENE (piroxicam).
For good reasons:

- it's effective—proven relief of the pain and inflammation of rheumatoid arthritis and osteoarthritis in millions of patients, in 80 countries all around the world.
- it's efficient—once daily, 20-mg dose provides round-the-clock relief, improves compliance and remains effective during long-term therapy, maintaining 24-hour therapeutic blood levels once steady state is reached in 7 to 12 days.
- it's preferred—in an open multi-center study, the antiarthritic preferred by physicians for their patients was FELDENE.[1]

Feldene® (PIROXICAM) 20 mg capsules

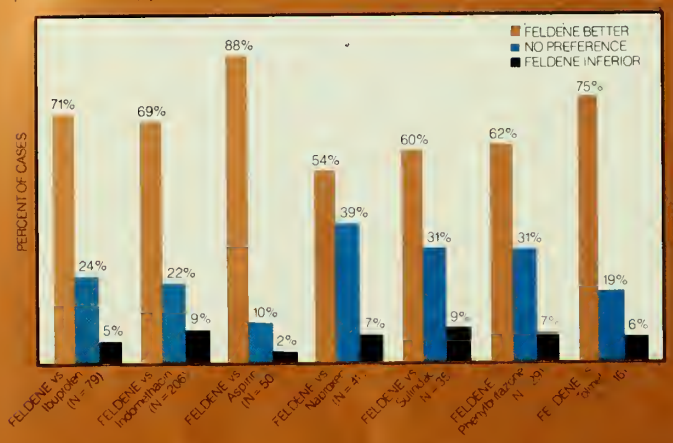
ONE-A-DAY

Please see a brief summary of FELDENE (piroxicam) prescribing information on the following page.

Feldene®
(PIROXICAM) 20 mg capsules

Rated better by physicians in an open multicenter trial

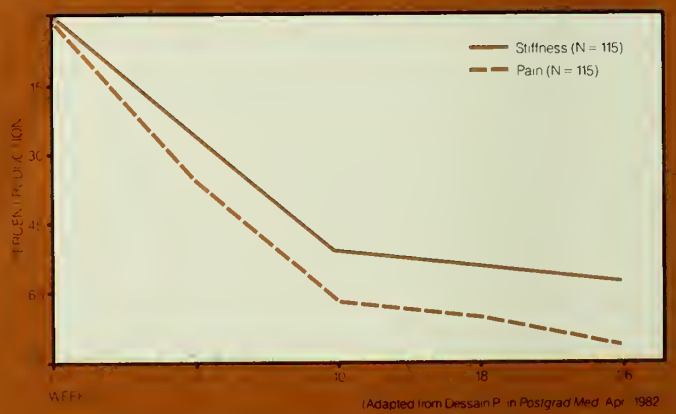
INVESTIGATORS' COMPARATIVE GLOBAL EVALUATIONS
(Physicians rated Feldene therapy as "better than," "equal to," or "inferior to" previous therapy based on global evaluations of patients' overall response.)



(Adapted from Dessain P. in *Postgrad Med*, Apr. 1982)

Investigators' global comparisons of Feldene and previous medications in multicenter open trials by 156 physicians in 749 osteoarthritis patients who had been on previous drug therapy. The above chart includes only those drugs available in the U.S. Average FELDENE dose was 20 mg/day.

REDUCTION IN PAIN AND STIFFNESS
Patients with osteoarthritis evaluated over 6 months on Feldene (mean dose of 20 mg/day) therapy showed dramatic reduction in pain and stiffness.



(Adapted from Dessain P. in *Postgrad Med*, Apr. 1982)

Multicenter long-term follow-up of 154 patients who had shown adequate response to piroxicam in short-term trials. 115 patients for whom complete data were available at every assessment visit through 26 weeks.

Reference

1. Dessain P. Efficacy and toleration of piroxicam in general practice. A multicenter study of osteoarthritis. *Postgrad Med* (special report) 76–81, April, 1982.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNING: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision. (See ADVERSE REACTIONS.)

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE. Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with Feldene. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE, increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia.

Dermatologic: pruritus, rash.

Central Nervous System: dizziness, somnolence, vertigo.

Urogenital: BUN and creatinine elevations (see PRECAUTIONS).

Body as a Whole: headache, malaise.

Special Senses: tinnitus.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

* Reactions occurring in 3% to 9% of patients treated with FELDENE (piroxicam).

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions.

Central Nervous System: depression, insomnia, nervousness.

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS).

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS).

Special Senses: swollen eyes, blurred vision, eye irritations.

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina.

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease.

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS).

Incidence Less Than 1%
(Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100 but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis.

Dermatologic: onycholysis, loss of hair.

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias.

Urogenital System: dysuria.

Body as a Whole: weakness.

Cardiovascular/Respiratory: palpitations, dyspnea.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis. It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CLINICAL PHARMACOLOGY IN OBSTETRICS—Edited by Peter Lewis, MD, PhD, FRCP, Director, Merrell Dow Research Centre, Strasburg, France. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 378 pages, $39.50.

CRITICAL CARE OF THE OBSTETRIC PATIENT—Edited by Richard L. Berkowitz, MD, Professor, Department of Obstetrics and Gynecology, The Mount Sinai School of Medicine, and Director, Division of Maternal-Fetal Medicine, The Mount Sinai Hospital, New York. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 543 pages, $55.00.

CURRENT SURGICAL DIAGNOSIS & TREATMENT—6th Edition—Edited by Lawrence W. Way, MD, Professor of Surgery, University of California, San Francisco, School of Medicine, and Chief of Surgical Service, Veterans Administration Medical Center, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 1,187 pages, $28.00 (softbound).

FORENSIC MEDICINE: A Guide to Principles—Second Edition—I. Gordon, MB, ChB, FRSSAf, Hon MD(Natal), Hon LLD(S.A.), Emeritus Professor of Forensic Medicine, University of Natal, and Formerly Chief Government Pathologist, Durban, and Dean, Faculty of Medicine, University of Natal, 1955-1971; H.A. Shapiro, PhD, MB, ChB, FRSSAf, Hon LLD(Natal), Professor of Forensic Medicine, University of South Africa, Visiting Professor of Forensic Medicine, University of Natal, Former Government Pathologist, Cape Town. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 451 pages, $50.00.

THE HAND—EXAMINATION AND DIAGNOSIS—Second Edition—Amer-Cape Town. Churchill Livingston Inc., 1560 Broadway, New York, NY Broadway, New York, NY 10036, 1983. 112 pages, $9.95 (paperback).

HANDBOOK OF DERMATOLOGIC TREATMENT—R. Kenneth Landow, MD, Assistant Clinical Professor of Medicine (Dermatology), University of Southern California School of Medicine, Los Angeles. Jones Medical Publications, 355 Los Cerros Dr., Greenbrae, CA 94904, 1983. 219 pages, $13.95.

HIRSUTISM AND VIRILISM—PATHOGENESIS AND MANAGEMENT—Edited by Virendra B. Mahesh, Regents' Professor and Chairman, and Robert B. Greenblatt, MD, Professor Emeritus, Department of Endocrinology, Medical College of Georgia, Augusta. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 394 pages, $49.50.

IMMUNE CYTOPENIAS—Volume 9 in Methods in Hematology—Edited by Robert McMillan, MD, Director, Weingart Center for Bone Marrow Transplantation, and Member, Department of Basic and Clinical Research, Scripps Clinic and Research Foundation, La Jolla, California. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 223 pages, $45.00.

IMMUNOASSAYS FOR CLINICAL CHEMISTRY—2nd Edition—Edited by W. M. Hunter, PhD, and J. E. T. Corrie, PhD, MRC Immunoassay Team, Edinburgh. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 701 pages, $75.00.

MIGRAINE AND ITS VARIANTS—George Selby, MD, FRCP(London,) FRCP (Edinburgh), FRACP, Visiting Neurologist, Royal North Shore Hospital, Sydney, Australia. John Wright • PSG Inc., 545 Great Rd., Littleton, MA 01460, 1983. 149 pages, $20.00.

THE MIGRAINE PREVENTION COOKBOOK—Josie A. Wentworth. Doubleday & Company, Inc., 245 Park Ave., New York, NY 10017, 1983. 194 pages, $13.95.

MUSCULOSKELETAL TUMOR SURGERY—Volumes 1 and 2—William F. Enneking, MD, Distinguished Service Professor and Eugene L. Jewett, Professor of Orthopaedic Surgery, Department of Orthopaedics, College of Medicine, University of Florida, Gainesville. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 1,562 pages, $250.00.

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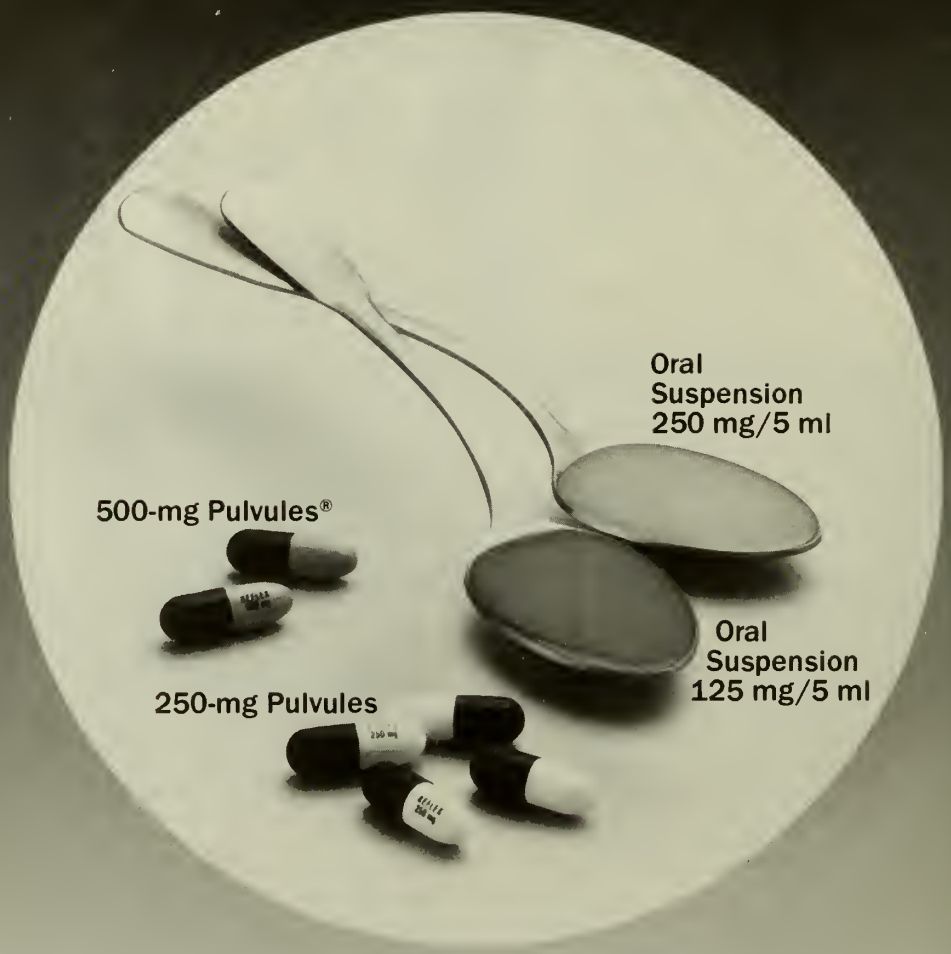

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Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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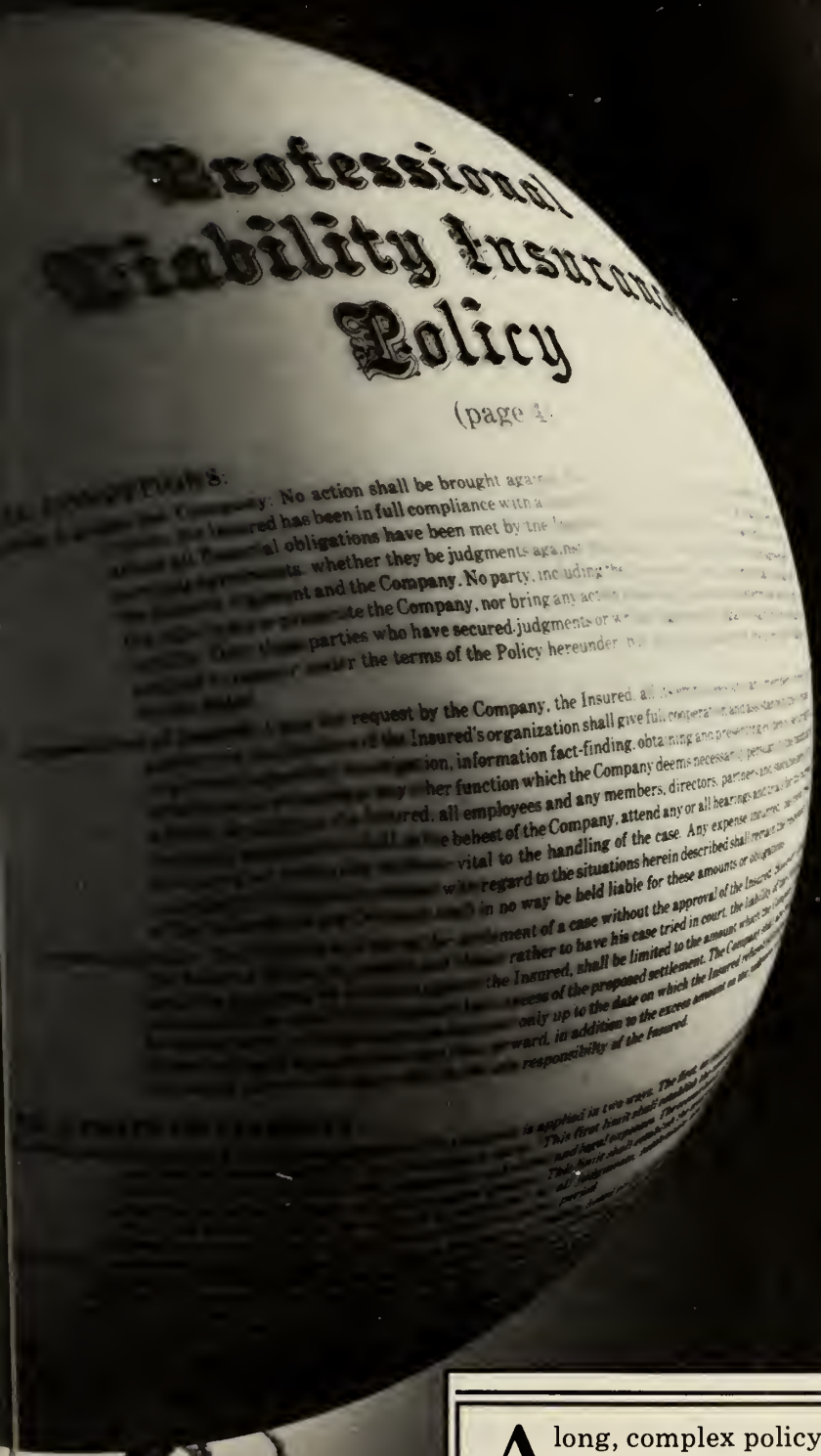

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ALLERGY AND IMMUNOLOGY

June 13-15—**Contemporary Aspects of Clinical Immunology.** American Society of Clinical Pathologists at San Diego. Wednesday-Friday. 18.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Monday-Thursday. $375.

October 24-28—**American Association for Clinical Immunology and Allergy Meeting** at San Diego. Wednesday-Sunday. Contact: Howard S. Silber, Exec. Dir., PO Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

October 25-28—**Allergy, Immunology and Infectious Disease.** Symposium Maui, Inc. and Hawaii Chapter American Academy of Family Physicians at Maui Marriott, Kaanapali, Maui. Thursday-Sunday. 18 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., PO Box 10185, Lahaina, Maui, HI 96761. (808) 661-8032.

ANESTHESIOLOGY

June 14-17—**Annual Scientific Meeting of the California Society of Anesthesiologists** at Disneyland Hotel, Anaheim. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

August 17-21—**Clinical Neuroanesthesia Conference.** UCSD at InterContinental Hotel, San Diego. Friday-Tuesday. 22 hrs.

September 28-30—**Anesthesia Practice 1984.** Anesthesiology Education Foundation at Monterey. Friday-Sunday. 10½ hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles 90024.

CANCER

May 18-20—**The Primary Care Physician and Cancer.** UCSD at Vacation Village, San Diego. Friday-Sunday.

(Continued on Page 709)

KEY TO ABBREVIATIONS

CMA: California Medical Association
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DREW: Charles R. Drew Postgraduate Medical School
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LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

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STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
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UCSD: University of California, San Diego
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Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

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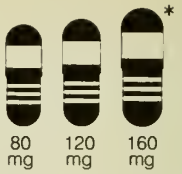

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INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmia is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the platelets of man

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient but there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm

Propranolol is not significantly dialyzable
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL
WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol
PRECAUTIONS. *General* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia, congestive heart failure; intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

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New York, N.Y. 10017

(Continued from Page 705)

June 15—**Cancer Precursors of the Cervix, Vagina and Vulva: An Overview of Pathogenesis and Management.** UCD at Red Lion Inn, Sacramento. Friday.

June 22—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. $135. Contact: J. Shiller, CMEA, PO Box 94296, San Diego 92138. (619) 223-2997.

June 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 18-20—**8th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. $300. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

CARDIOLOGY

May 18-20—**Decision Making in Congenital Heart Disease.** Children's Hospital and Health Center and Donald N. Sharp Memorial Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Sunday. 18 hrs. $350. Contact: Congenital Heart Disease, PO Box 9494, San Diego 92109. (619) 272-3126.

May 21-22—**Advanced Cardiac Life Support.** See Emergency Medicine, May 21-22.

June 10-13—**Advanced Echocardiography—1984: Interactions with NMR, Digital Angiography and CT Scanning.** American College of Cardiology at San Diego. Sunday-Wednesday. Contact: Reg. Sec. Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 20—**Coronary Artery Disease Symposium.** UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday. 7 hrs.

June 22-24—**ECG Interpretation, Arrhythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at Lake Tahoe. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 22-24—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Scott and Klamath Rivers. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

June 25-27—**Cardiac Morphology: Echocardiographic, Nuclear Imaging, Necropsy Correlations.** American College of Cardiology and Indiana University School of Medicine at Hyatt Lake Tahoe, Incline Village. Monday-Wednesday. Contact: Reg. Sec., Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 25-29—**National Board Review Course in Pulmonary Medicine.** American College of Chest Physicians at Sheraton Palace Hotel, San Francisco. Monday-Friday. 28 hrs. Contact: Dept. of Ed., ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (312) 698-2200.

July 7-14—**Cardiovascular Medicine and Surgery and Critical Care Medicine.** STAN at Mauna Kea Beach Hotel, Kamuela. One week.

August 12-17—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

August 17-19—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 24-26—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress and Holter) and Cardiac Resuscitation.** International Medical Education Corporation at Monterey. Friday-Sunday. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 14-16—**ECG Interpretation, Arrhythmia, and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 15-22—**Hawaiian Echocardiography Course.** Institute for Medical Studies at Hawaiian Islands. One week. 20 hrs. $295. Contact: IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

September 20-22—**Recent Advances in Pulmo-**

nary and **Critical Care Medicine.** UCSF at Meridien Hotel, San Francisco. Thursday-Saturday.

October 7-10—**Cardiology Course**. UCSF at Yosemite. Sunday-Wednesday.

October 15-19—**Pulmonary Medicine Review 1984.** USC. Monday-Friday. $450.

October 26-28—**ECG Interpretation, Arrythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at San Francisco. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

EMERGENCY MEDICINE

May 21-22—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

May 29-June 2—**Gateway to Knowledge.** Society of Critical Care Medicine at San Francisco. Tuesday-Saturday. Contact: SCCM, 223 E. Imperial Hwy, Ste. 110, Fullerton 92635. (714) 870-5243.

June 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 33 hrs.

June 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton Wharf, San Francisco. Monday-Friday. $425.

July 4-5—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Salmon River. Wednesday-Thursday. 10 hrs. $245. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

July 6-8—**Trauma and CPR Update—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 10-13—**Emergency Medicine: A Critical Appraisal.** California Chapter American College Emergency Physicians and Emergency Medical Associates at Ramada Inn at Fisherman's Wharf, San Francisco. Tuesday-Friday. 20 hrs. $360. Contact: Seminars International, Dept. A, 15910 Ventura Blvd., Ste. 731, Encino 91436.

July 16-20—**Postgraduate Institute for Emergency Physicians.** UCSD. Monday-Friday. 33 hrs.

July 30-31—**Advanced Cardiac Life Support.** Emergency Care Education Center, Emergency Department Physicians, and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina Del Rey 90291. (213) 822-1312.

August 3-5—**Whitewater Raft Conference: Trauma Evaluation and Treatment.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** American College of Obstetrics and Gynecology at Hotel del Coronado, Coronado. Wednesday-Friday. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 24-26—**Wilderness Emergency Care—Mt. Shasta Summit Expedition.** Mercy Medical Center, Redding at Mt. Shasta. Friday-Sunday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 27-31—**Topics in Emergency Medicine.** UCSF at San Francisco. Monday-Friday. $425.

September 1-3—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Klamath River. Saturday-Monday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

September 6-7—**Burns: Emergency and Acute Care.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Friday.

September 17-21—**Postgraduate Institute for E.R. Physicians, Symposium I.** UCSD at InterContinental Hotel, San Diego. Monday-Friday. 36 hrs.

September 28-29—**Advanced Trauma Life Sup-**

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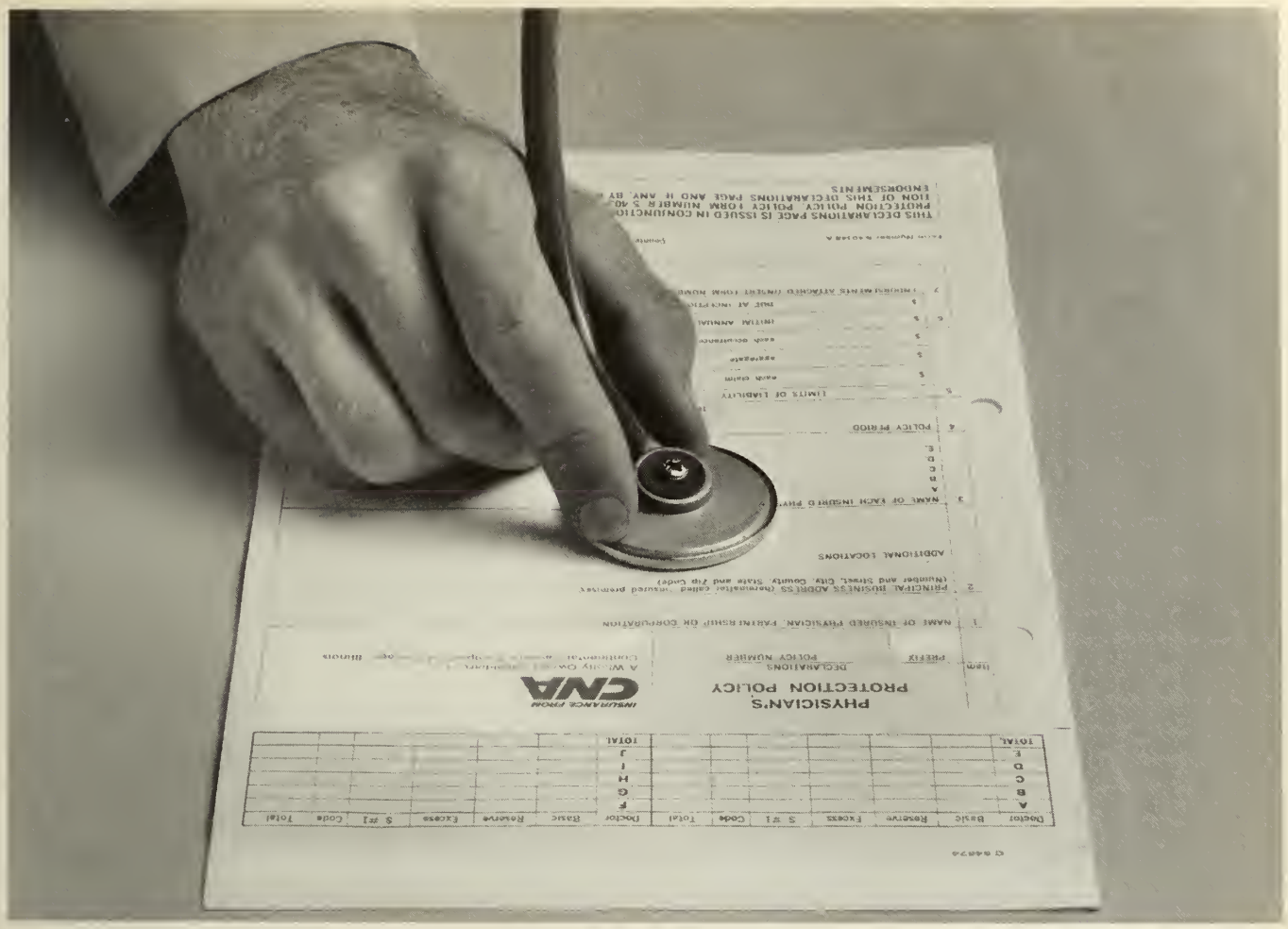

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(Continued from Page 710)

port Provider Course. Emergency Shock Trauma Institute, Mercy Hospital at San Diego. Friday-Saturday. 16 hrs. $475. Contact: Emergency Shock Trauma Institute, Mercy Hospital, 4077 5th Ave., San Diego 92103. (619) 294-8111.

October 29-30—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

October 31-November 2—**EMS Today.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 19 hrs.

INTERNAL MEDICINE

May 20-26—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** American Institute of Primary Care Medicine, University of Arizona College of Medicine at Napa Valley. One week. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

June 13-15—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Stanford Court Hotel, San Francisco. Wednesday-Friday. $375.

June 18-22—**Advances in Internal Medicine.** UCSF. Monday-Friday. $465.

June 22-24—**Update on Cardiovascular Drugs—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 7-14—**32nd Annual Intensive Review of Internal Medicine.** USC. One week. $475.

July 20-22—**Infectious Disease.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 29-August 1—**Biomedical Ethics—Wilder-**

(Continued on Page 717)

RU-TUSS® II

sustained release capsules

Before prescribing, see complete prescribing information. The following is a brief summary.

DESCRIPTION: Each sustained release capsule contains 12 mg of chlorpheniramine maleate, USP and 75 mg of phenylpropanolamine hydrochloride, USP in a base to provide prolonged activity.

INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).

CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.

WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.

Usage in pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.

PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.

ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with chlorpheniramine maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, hypertension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis, leukopenia.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis hysteria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.

OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.

HOW SUPPLIED: Green and clear capsules with green and white beads. Bottles of 100 tablets. NDC 0524-0031-01
Store at controlled room temperature 15-30°C (59°-86°F.).

CAUTION: Federal law prohibits dispensing without prescription.

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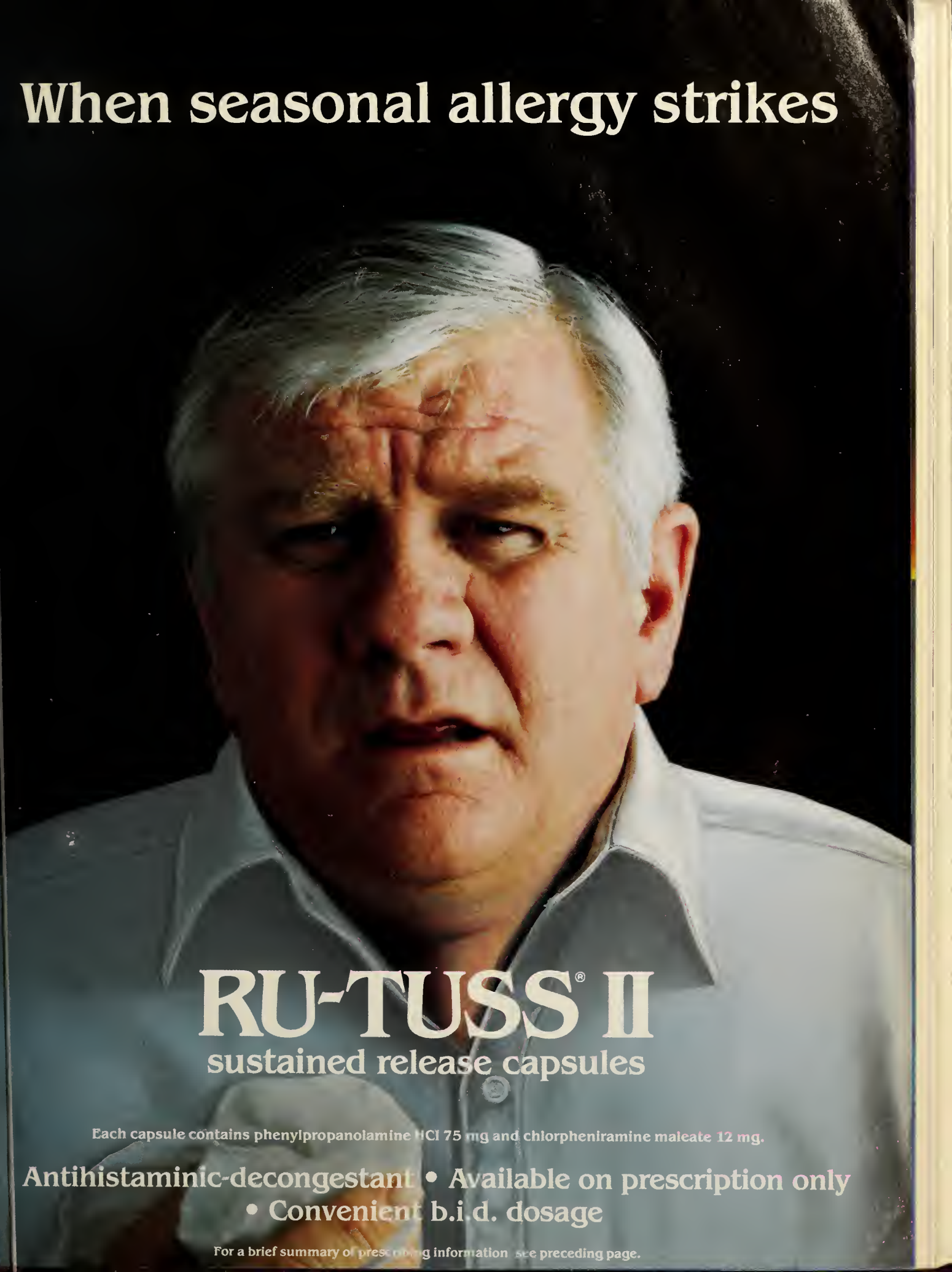
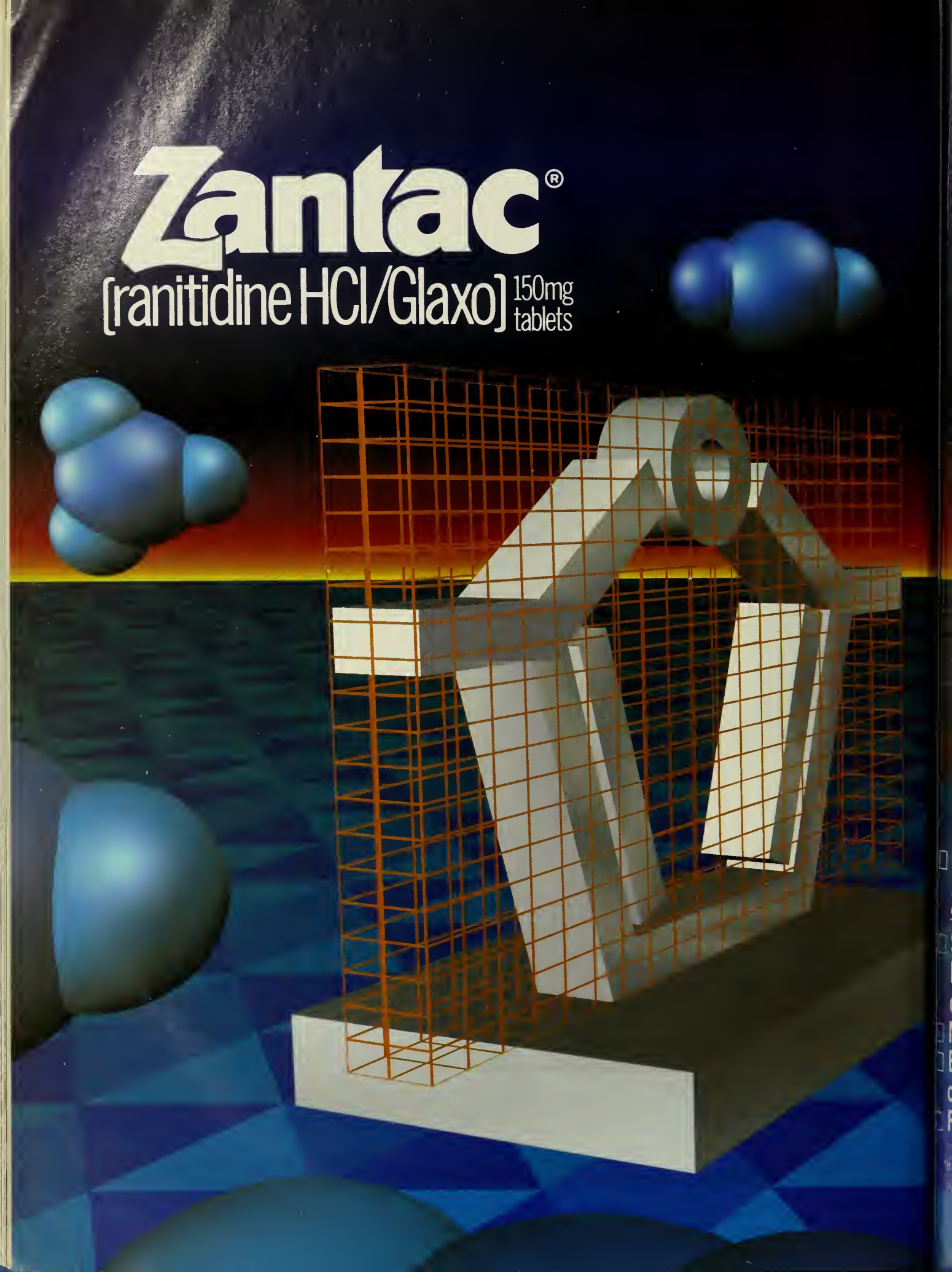
Pioneers in medicine for the family

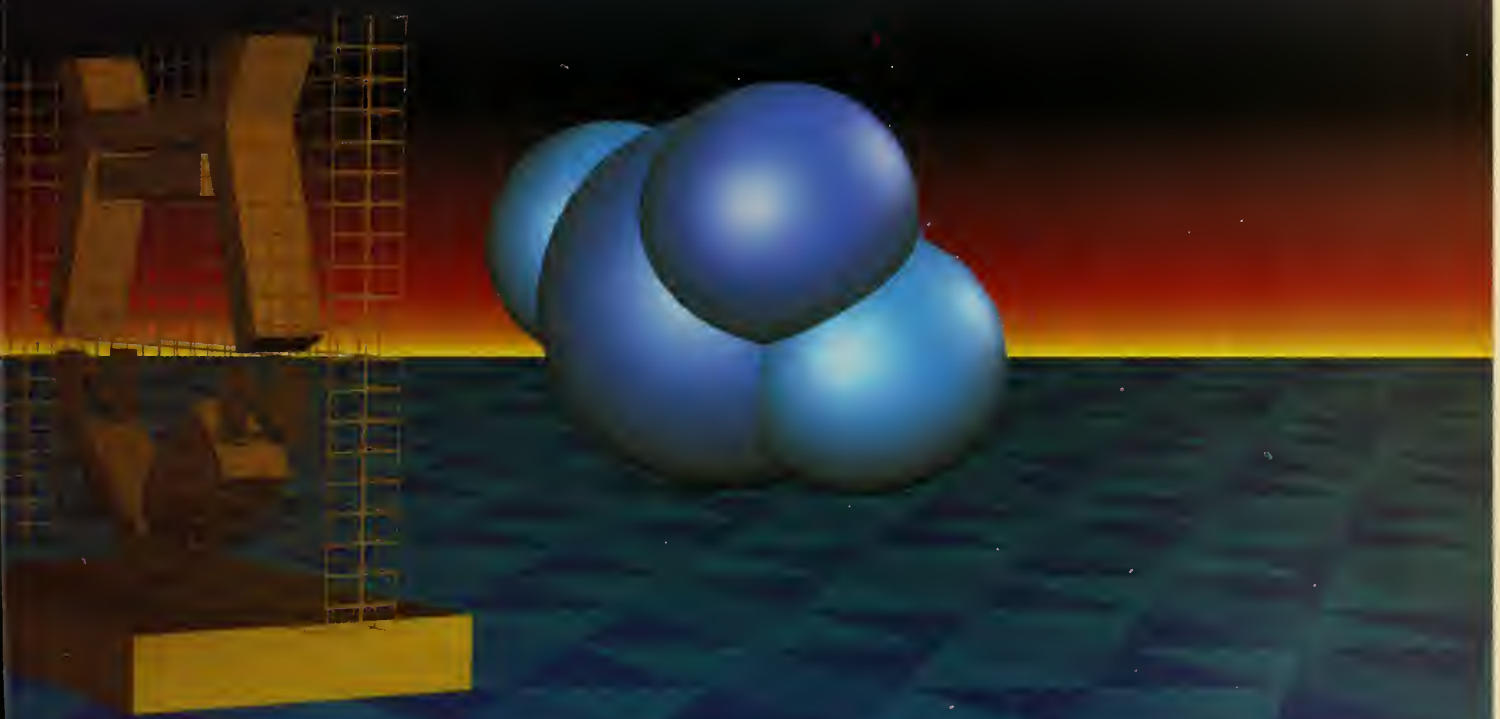
When seasonal allergy strikes




Zantac®
[ranitidine HCl/Glaxo] 150mg tablets

Glaxo ROCHE

Unsurpassed activity in gastric acid inhibition: for active duodenal ulcer and pathological hypersecretory conditions*



Zantac is a new chemical compound

- Not a histamine-related imidazole—a furan compound.

Zantac offers important patient benefits

- Single-dose action for up to 12 hours—b.i.d. administration. Four weeks of therapy for most patients with active duodenal ulcer.
- No interaction with warfarin, theophylline and diazepam.
- Effective and well tolerated even in pathological hypersecretory conditions.
- For adverse reactions see complete prescribing information.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers.

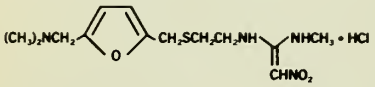
Please see following page for complete prescribing information.

Unsurpassed activity in gastric acid inhibition

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTION: The active ingredient in ZANTAC* Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLOGY: ZANTAC* (rantidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. **Effects on acid secretion:**
ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC* on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg 75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. **Effects on other gastrointestinal secretions:**
Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.
Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. **Other pharmacological actions:**
a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. **Pharmacokinetics:**
ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:
Duodenal Ulcer
In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC*-treated patients as shown below:

	ZANTAC* + Number Entered	Healed/ Evaluable	Placebo + Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid Ulcer Healed	Ulcer Not Healed
ZANTAC*	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIONS AND USAGE:
ZANTAC* (ranitidine hydrochloride) is indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC* (ranitidine hydrochloride).

PRECAUTIONS:
General
1. Symptomatic response to ZANTAC* therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests
False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction
Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility
There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and fats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, E. Coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy
Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC* (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in children have not been established.

Use in Elderly Patients
Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS
Headache has been found to be more frequent in ZANTAC®-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC® in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:
Duodenal Ulcer
The current recommended adult oral dosage of ZANTAC* for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function.
On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED
ZANTAC* Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Issued Sept. 1983

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

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ness Horseback Conference. Mercy Medical Center, Redding at Trinity Alps Wilderness. Sunday-Wednesday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 17-19—**2nd Annual La Jolla Summer Conference on Dermatology, Immunology and Rheumatology.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. Contact: Dianne Tisue, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

September 10-15—**6th Comprehensive Nephrology Review Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Saturday. 38.5 hrs. $695.

September 15—**Neurology.** UCSF at Fresno. Saturday.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 19—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. Contact: Charles R. Beeson, MD, Assoc. Chief of Staff for Ed., VA Medical Center, 16111 Plummer St., Sepulveda 91343. (818) 891-2374.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** See Allergy and Immunology, October 15-18.

OBSTETRICS AND GYNECOLOGY

May 30-June 2—**Controversies in Obstetrics and Gynecology.** Memorial Hospital Medical Center and UCI at Silverado Country Club and Resort, Napa. Wednesday-Saturday. 20 hrs. Contact: Asst. Dir., Center for Health Ed., 2801 Atlantic Ave., Long Beach 90801-1428.

June 15—**Cancer Precursors of the Cervix, Vagina and Vulva: An Overview of Pathogenesis and Management.** See Cancer, June 15.

June 21-23—**Gynecologic Surgery: Principles and Techniques.** See Surgery, June 21-23.

October 7-9—**The Neural and Metabolic Bases of Feeding.** See Pediatrics, October 7-9.

August 9-11—**Basic and Advanced Colposcopy.** American College of Obstetrics and Gynecology at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

OPHTHALMOLOGY

June 7-8—**Practical Office Management of Corneal, External Diseases and Uveitis.** UCSF at Hyatt Regency, San Francisco. Thursday-Friday.

June 8-9—**Microsurgery and Laser Techniques for Glaucoma.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 14 hrs. $500. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024.

June 14-16—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. 18 hrs. $750. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024.

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** See Pediatrics, June 29-30.

PEDIATRICS

May 16—**Los Angeles Pediatric Society Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** See Psychiatry, May 17-18.

May 26-28—**1984 Annual Spring Meeting Northern California Chapter American Academy of Pediatrics** at Hyatt Del Monte, Monterey. Sat-

urday-Monday. 11 hrs. Contact: AAP, 1125 A St., Ste 210, San Rafael 94901. (415) 459-4775.

June 8-9—**Fantasy Broken: Infant and Toddler Abuse.** UCI. Friday-Saturday. 11 hrs.

June 13—**Seizure Disorders in Infancy and Childhood.** LLU. Wednesday. 4 hrs. $50.

June 28-30—**9th Annual Meeting of the Society for Pediatric Dermatology.** STAN at Caesar's Tahoe, Lake Tahoe. Thursday-Saturday.

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Saturday. 8 hrs. $100.

October 3-4—**41st Annual Brenneman Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Red Lion Motor Inn, Sacramento. Sunday-Tuesday.

PSYCHIATRY

May 17-18—**Child Abuse: Behavioral and Developmental Consequences.** UCD at Holiday Inn Holidome, Sacramento. Thursday-Friday.

May 19—**Conception and Misconceptions of Structural Family Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 19-20—**Freud-Jung Symposium: Clinical Issues.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday.

June 8—**8th Annual Psychiatry Symposium.** Southern California Kaiser-Permanente Medical Group at Newport Beach Marriott Hotel. Friday. 6 hrs. $100. Contact: Dept. of Clinical Services, SCKPMG, 4747 Sunset Blvd., Los Angeles 90027.

June 9—**Brief Therapy with Child and Adolescent Problems.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

June 16—**Clinical Decision-Making with Couples and Families.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

June 18-22—**Divorce Mediation.** Mental Research Institute, Palo Alto. Monday-Friday. 20 hrs. $195. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 14—**The Interactional Treatment of Eating Disorders.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $95. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 20-21—**Human Sexuality for the Health Professional.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 23-27—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 28—**Treating Depression in a Marital Context.** Mental Research Institute. Palo Alto. Saturday. 5 hrs. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 29-August 2—**Mental Research Institute Summer Seminar** at Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-8—**Basic Hypnotherapy: Principles and Applications.** Mental Research Institute, Palo Alto. Monday-Wednesday. 6 hrs. $65. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-10—**Brief Therapy.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $175. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 13-16—**Family Crisis: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 18-23—**Responsibility Issues in Mental Health.** Southern California Psychiatric Institute at Mauna Kea Beach Hotel, Kauela, HI. Saturday-Thursday. 15 hrs. Contact: Gail Waldron, MD, Program Dir., SCPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

August 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

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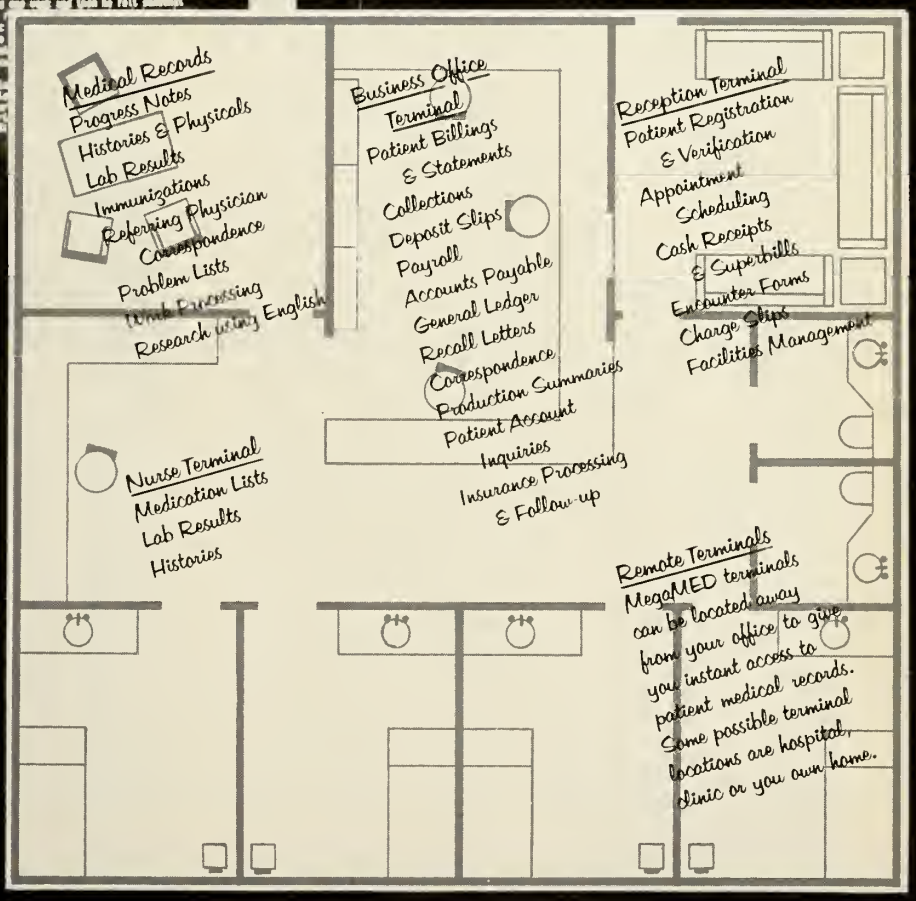

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(Continued from Page 718)

August 25—**Case Studies in Brief Interactional Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

RADIOLOGY AND PATHOLOGY

May 22-25—**Present Concepts in Diagnostic Radiology.** Letterman Army Medical Center, San Francisco. Tuesday-Friday. 26 hrs. Contact: R. S. Pakusch, MD, Program Chairman. (415) 561-3764.

June 8-10—**9th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $290. Contact: Richard A. Oas, MD, SDUC, c/o LARS, 5200 Century Blvd., Ste. 920, Los Angeles 90045. (213) 484-5120.

June 10-16—**4th Annual Post Conference Seminar.** American College of Radiology at Silverado Country Club, Napa Valley. One week. 20 hrs. $350. Contact: Richard A. Oas, MD, SDUC, c/o LARS, 5200 Century Blvd., Ste. 920, Los Angeles 90045. (213) 484-5120.

June 13-15—**Contemporary Aspects of Clinical Immunology.** American Society of Clinical Pathologists at San Diego. Wednesday-Friday. 18.5 hrs. Contact: Regional Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

June 17-22—**Pathology of the Lung.** UCSD. Sunday-Friday. 50 hrs.

August 20-24—**Radiology of the Abdomen.** UCSD at San Diego and Anaheim. Monday-Friday. 27 hrs. $395.

August 27-29—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and Northern California Radiological Society at Napa Valley. Monday-Wednesday. 18 hrs. $325. Contact: Michael H. Reid, MD, Program Dir., SRREF, PO Box 19184, Sacramento 95819.

September 6-9—**Radiology Physics Review Course.** UCD at Sacramento. Thursday-Sunday.

September 17-20—**American College of Radiology Meeting** at Century Plaza Hotel, Los An-

(Continued on Page 724)

References:
1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
PRDCARDIA* (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PRDCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PRDCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PRDCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PRDCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCAROIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PRDCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PRDCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PRDCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PRDCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PRDCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PRDCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PRDCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PRDCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PRDCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PRDCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PRDCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PRDCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. © 1982, Pfizer Inc.

Pfizer LABORATORIES DIVISION
PFIZER INC

"I can do things that I couldn't do for 3 yrs. including joining the human race again."

Quotes from an unsolicited letter received by Pfizer from an angina patient.
While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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"My daily routine consisted of sitting in my chair trying to stay alive."

"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

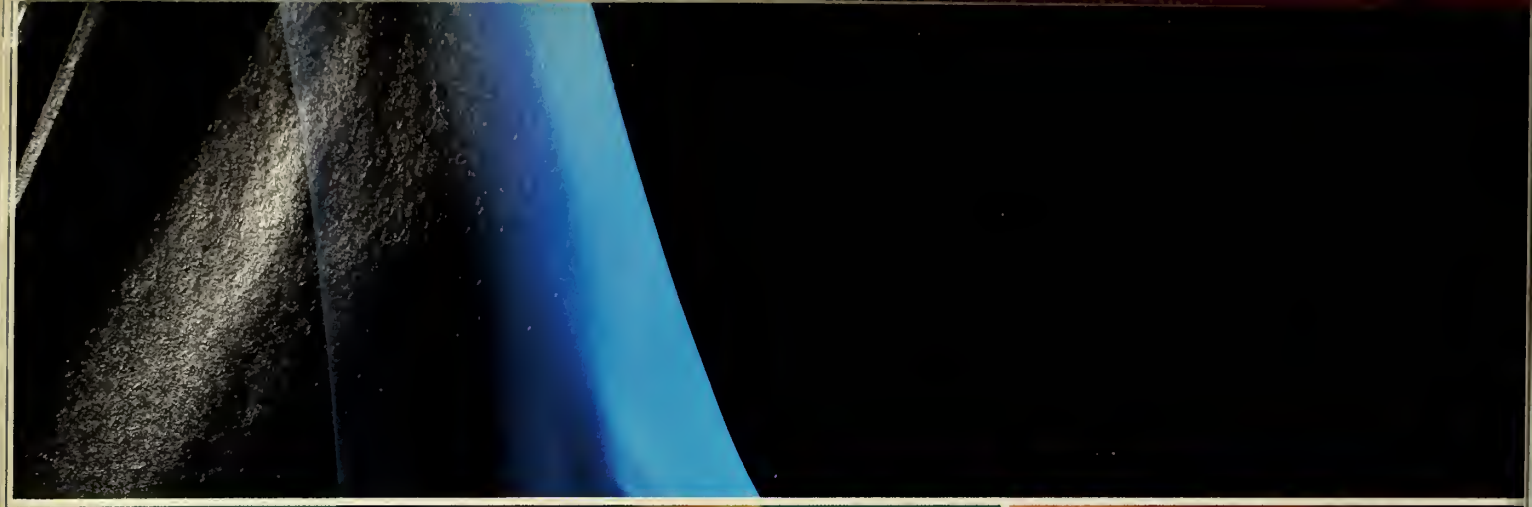
Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

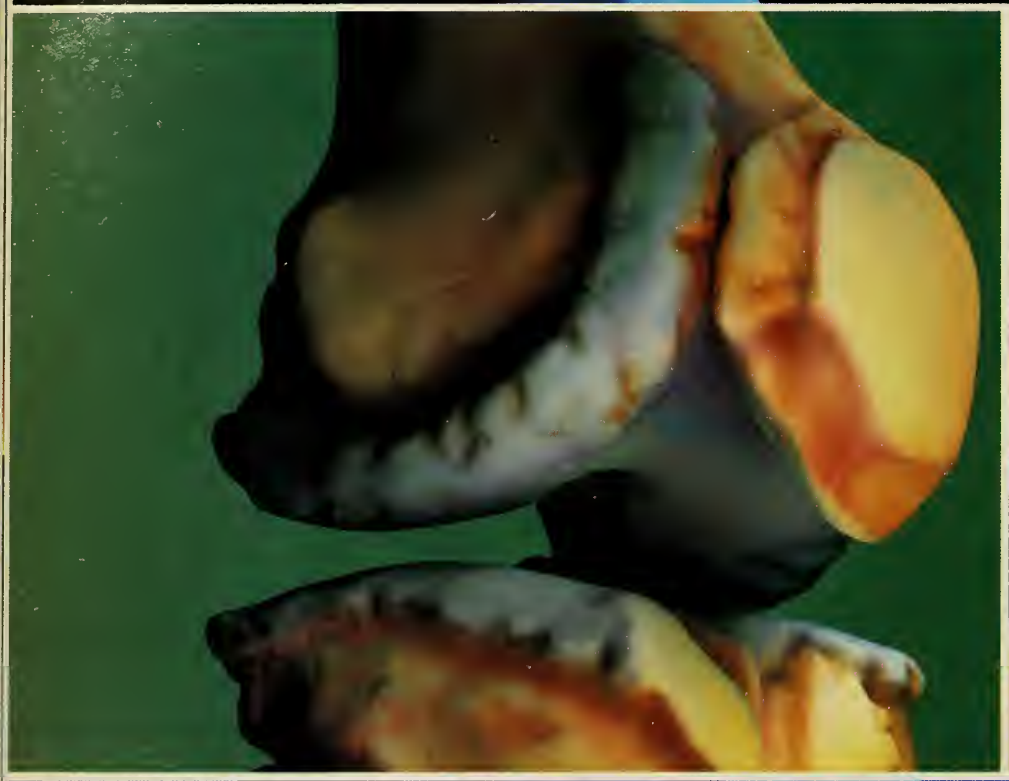
for the varied faces of angina

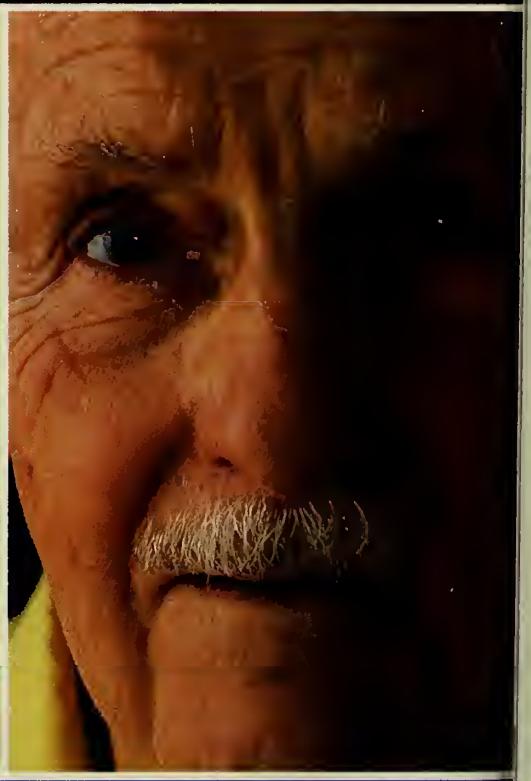
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*







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Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

Advanced age has little or no influence on the pharmacokinetics of *Motrin*.

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

Helping you to help your patients—
Ask your Upjohn Representative for a complimentary supply.

The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS
(ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.
Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.
Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.
The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.
Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.
Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.
Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.
Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence less than 1%—Probable Causal Relationship*
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence less than 1%—Causal Relationship Unknown*
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.
*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
Caution: Federal law prohibits dispensing without prescription.

Motrin is a registered trademark of The Upjohn Manufacturing Company M, Barceloneta, Puerto Rico

MED B-7-S

Upjohn

(Continued from Page 720)

geles. Monday-Thursday. Contact: ACR, 20 N. Wacker Dr., Chicago 60606. (312) 236-4963.

October 13-21—**9th Annual International Body Imaging Conference.** West Park Hospital at Royal Lahaina Hotel, Maui. One week. 28 hrs. $425. Contact: Conference Sec., 9th Annual Body Imaging Conf., Dept. of Radiology, West Park Hospital, 22141 Roscoe Blvd., Canoga Park 91304. (818) 340-0580, ext. 280.

October 22-26—**9th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Monday-Friday.

SPORTS MEDICINE

May 23-26—**American College of Sports Medicine Meeting** at Town and Country Hotel, San Diego. Monday-Thursday. Contact: T. Miller, Exec. Dir., ACSM, 1440 Monroe St., Madison, WI 53706.

June 14-16—**Knee Problems in Athletes.** American Academy of Orthopaedic Surgeons at Monterey. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

June 24-27—**Marine Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Wednesday.

July 20-22—**Sports Medicine and Cardiovascular Fitness—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 23-26—**10th Annual Meeting of American Orthopaedic Society for Sports Medicine** at Marriott Hotel, Anaheim. Monday-Thursday. Contact: AOSSM, PO Box 94274, Chicago 60690.

SURGERY

May 21-25—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 1-3—**Failed Arthroplasty Revision and Salvage.** American Academy of Orthopaedic Surgeons at San Francisco. Friday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

(Continued on Page 726)

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(Continued from Page 724)

June 4-8—**Microsurgery Training Workshop.** Microsurgery Education and Research Foundation at La Jolla Village Inn, La Jolla. Monday-Friday. 35 hrs. $1,300. Contact: Hazel Sayers, Workshop Coord., PO Box 22514, San Diego 92122.

June 8-9—**Prosthetics/Orthopedics.** UCD at Holiday Inn Holidome, Sacramento. Friday-Saturday.

July 9-13—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

June 9-14—**Fingers to the Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Saturday-Thursday.

June 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 20-24—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Regency, Maui. Wednesday-Sunday. Contact: WTSA, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

June 21-23—**Gynecologic Surgery: Principles and Techniques.** American College of Obstetrics and Gynecology at Silverado, Napa. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

June 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 28-29—**5th Annual Trauma Seminar.** DREW at Disneyland Hotel, Anaheim. Thursday-Friday. 16 hrs. $175.

July 7-14—**Cardiovascular Medicine and Surgery and Critical Care Medicine.** See Cardiology, July 7-14.

August 13-17—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 17-21—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

September 20-22—**Microsurgery: An Introduction to Microtechnique for Small Artery and Nerve Repair.** American Academy of Orthopaedic Surgeons at San Diego. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

October 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

October 9-14—**American Society of Plastic and Reconstructive Surgeons Inc., American Society of Maxillofacial Surgeons Inc. and Plastic Surgery Educational Foundation Meeting** at Las Vegas. Tuesday-Sunday. Contact: ASPRS-PSEF, Exec. Office, 233 N. Michigan Ave., Ste. 1900, Chicago 60601.

October 10-14—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. 34 hrs. $1,200.

October 11-13—**Controversies in Urology.** American Urological Association at San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, PO Box 25147, Houston, TX 77265. (713) 799-6070.

October 14-18—**Western Orthopedic Association Meeting** at San Diego. Sunday-Thursday. Contact: WOA, 1970 Broadway, Ste. 1235, Oakland 94612. (415) 893-1257.

October 21-26—**American College of Surgeons Meeting** at San Francisco. Sunday-Friday. Contact: ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 27—**Lumbar Spine and Pelvis.** UCSD at Hotel del Coronado, Coronado. Saturday.

October 28-November 9—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

May 18-20—**The Primary Care Physician and Cancer.** See Cancer, May 18-20.

May 19-20—**12th Annual Family Practice Sym-**

(Continued on Page 728)

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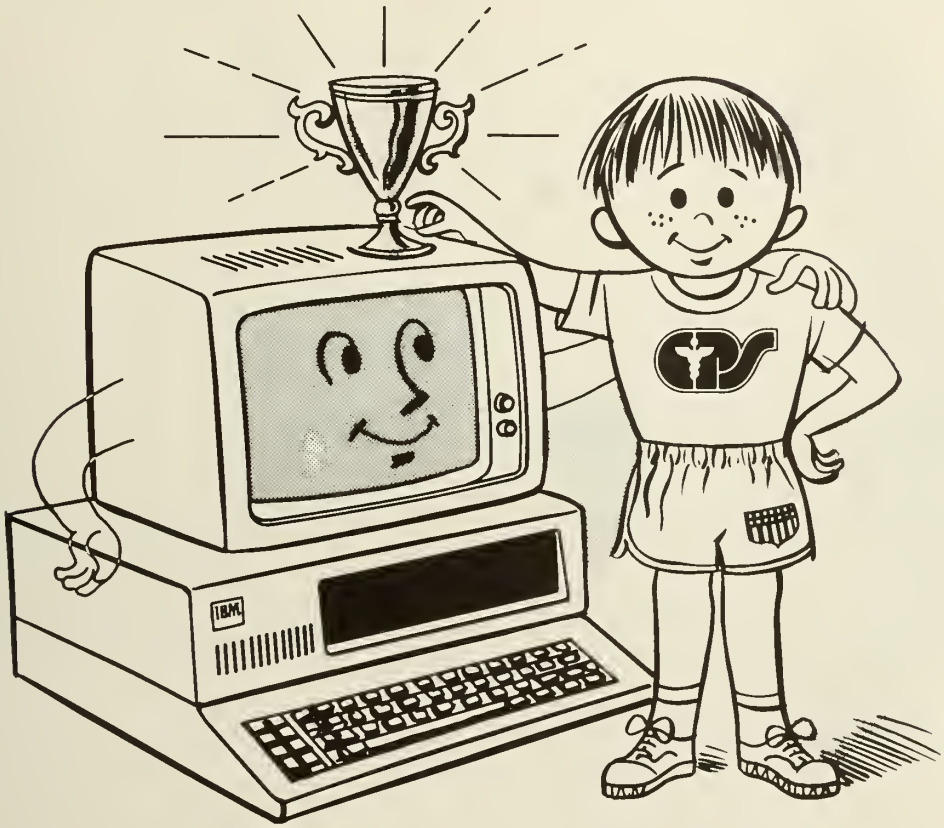

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(Continued from Page 726)

posium. Southern California Permanente Medical Group at Sheraton Universal Hotel, North Hollywood. Saturday-Sunday. 11 hrs. Contact: SCPMG, Dept. of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

May 20-24—**Family Practice Refresher Course.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Thursday.

May 21-26—**Intensive Review Course in Family Medicine.** DREW at Disneyland Hotel, Anaheim. Monday-Saturday.

May 29-June 2—**11th Annual UCLA Santa Monica Hospital Medical Center Family Practice Refresher Program.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Tuesday-Saturday. 35.5 hrs. $385.

June 1-12—**Southwestern Regional Cutaneous Flap Workshop.** Dermatology Research Foundation of California at UCLA. Friday-Saturday. 14 hrs. $495. Contact: Daniel E. Gormley, MD, 412 W. Carroll, Ste. 207, Glendora 91740.

June 2-3—**Eating Disorders: Current Perspectives on Assessment and Treatment.** UCLA. Saturday-Sunday. 13.5 hrs. $140.

June 5-8—**Society of Nuclear Medicine 31st Annual Meeting** at Los Angeles Convention Center. Tuesday-Friday. 36 hrs. Contact: Meetings Dept., SNM, 475 Park Ave. So., New York, NY 10016. (212) 889-0717.

June 8—**Occupational Medicine.** UCD at Beverly Garland Motor Lodge, Sacramento. Friday.

June 11-15—Review in Clinical Chemistry. American Society of Clinical Pathologists at Monterey. Monday-Friday. 35 hrs. Contact: Reg. Ed. Activities, 2100 W. Harrison St., Chicago 60612. (312) 738-1336, ext. 129.

June 14-16—**Postgraduate Institute—Geriatrics.** CMA at Hyatt, Lake Tahoe. Thursday-Saturday.

June 17-23—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center of Long Beach at Grand Hotel, Anaheim. One week. Contact: MMCLB, 2801 Atlantic Ave., Long Beach 90801. (714) 595-3811.

June 18-20—**Aluminum-Related Disease: Features, Pathogenesis, Recognition and Treatment and Prevention.** UCLA at The Newporter, Newport Beach. Monday-Wednesday. 20 hrs. $150.

June 20-24—**Golden State Medical Association Annual Scientific Session** at Hawaiian Regent Hotel, Oahu. Wednesday-Sunday. Contact: Lillian Fortier, GMSA, PO Box 2151 Station A, Berkeley 94702.

June 21-23—**1st Annual Superficial Anatomy and Cutaneous Surgery for Dermatologists: 1984.** UCSD. Thursday-Saturday. 22.5 hrs. $500.

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** See Pediatrics, June 29-30.

July 7-8—**Weekend with the Masters.** UCSD and Great Teachers Foundation at Double Tree Inn, Monterey. Saturday-Sunday. 20 hrs. $325. Contact: PO Box 61203, DFW Airport, TX 75261. (214) 659-4590.

July 10-12—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday. 22 hrs. $300.

August 1-4—**Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday.

August 17-19—**Nutrition, Obesity, and Weight Control—White Water Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

September 1—**Medical Mycology.** UCSF. Saturday.

September 13-14—**Intensive Course in Adolescent Obesity.** UCSF. Thursday-Friday. $135.

September 17-19—**Relational Issues of Addiction: Violence, Sexuality and Intimacy.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, Conf. Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

September 17-21—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

September 19-21—**State of the Art in the Care of Geriatric Patients: Pre-Intra-Post-Operative Management.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $325. Contact: Robin B. Jackson, Office of Cont. Ed., PO Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

(Continued on Page 818)

WMS JUNE 25-27, 1984

ANNUAL MEETING & PRACTICE MANAGEMENT SEMINARS

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Program

MONDAY, JUNE 25

7:45 am Registration/Exhibits

8:30 am WMS House of Delegates Opening Session

10:30 am Reference Committee Meetings

1:30 pm PRACTICE DEVELOPMENT TECHNIQUES
Conomikes Associates, Inc.

6:00 pm Welcome to the Tetons Social Hour

TUESDAY, JUNE 26

8:00 am Registration/Exhibits

8:30 am BETTER COLLECTIONS, BILLING AND INSURANCE METHODS
Conomikes Associates, Inc.

1:30 pm RECEPTION AND PATIENT-FLOW TECHNIQUES
Conomikes Associates, Inc.

6:00 pm President's Reception and Banquet

WEDNESDAY, JUNE 27

9:00 am WMS House of Delegates Closing Session

10:30 am Adjourn

WYOMING Medical Society

For Program, Reservations and Information Contact:

WYOMING MEDICAL SOCIETY
P.O. DRAWER 4009
CHEYENNE, WY 82003
Telephone (307) 635-2424

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide. dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

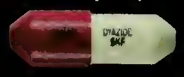
Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

The unique red and white Dyazide® capsule: Your assurance of SK&F quality.



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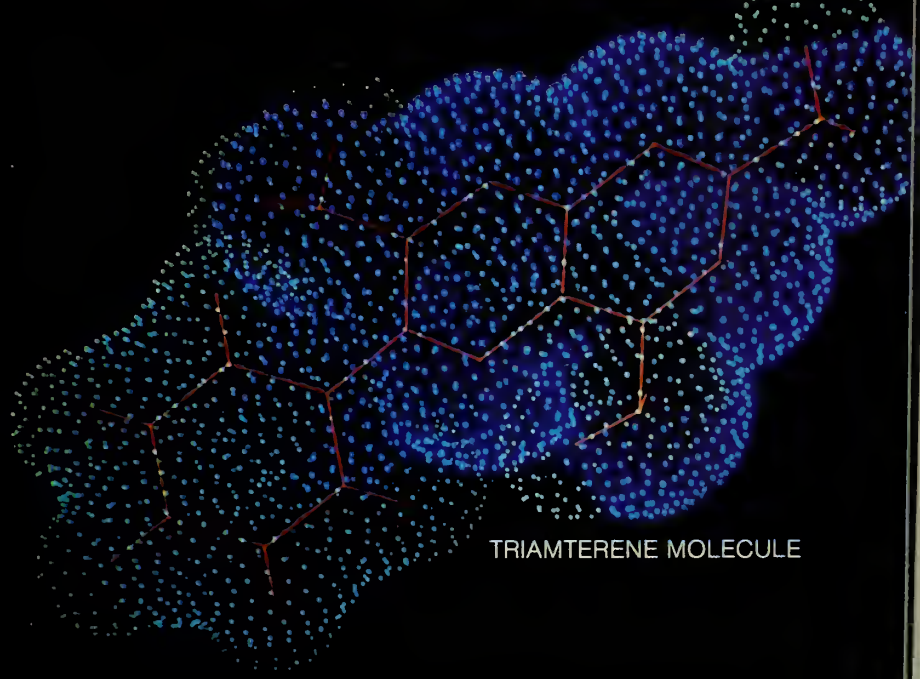
The Diuretic with a Difference



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Clinical Investigation

Immunogenicity of Hepatitis B Virus Vaccine (Heptavax-B)—Response of Healthy Adults

R. PALMER BEASLEY, MD, *and* LU-YU HWANG, MD, *Taipei, Taiwan*

We vaccinated 30 healthy adults who were susceptible to hepatitis B virus with 20 μg of Merck Sharp & Dohme vaccine at zero, one and six months and measured their antibody (anti-HBs) response weekly for four weeks and monthly for at least seven months. A month following the first dose 40% had antibodies and 90% were positive for anti-HBs a month following the second dose. The third dose raised the response rate to 93.3% but its major effect was to substantially raise the titer of virtually all of the vaccinees. Two persons had no antibody response to vaccination and four others were hyporesponders. No complications or significant side effects were observed.

(Beasley RP, Hwang L-Y: Immunogenicity of hepatitis B virus vaccine (Heptavax-B)—Response of healthy adults [Clinical Investigation]. West J Med 1984 May; 140:731-734)

Vaccines against hepatitis B virus infections have been under development for almost a decade. Two of the earliest are now licensed for commercial sale (Institute Pasteur, France, and Merck Sharp & Dohme, United States). They are prepared from hepatitis B surface antigen (HBsAg) purified from plasma of human HBsAg carriers. Several other purified HBsAg vaccines are also in the advanced stages of development and undergoing human testing but they are not yet commercially available. Initial studies in adults showed excellent immunogenicity with Merck Sharp & Dohme (MSD) vaccine (Heptavax-B) using a 40-μg dose administered at zero, one and six months.[1,2] This study was begun in October 1980 to evaluate whether a satisfactory immune response could be achieved with 20μg using the same three-dose schedule.

Subjects and Methods

Subjects

Participants were apparently healthy adult residents of Taiwan who gave written informed consent. Most were recent US State Department retirees. There were 30 whites and 6 Chinese; 22 men and 14 women. Ages ranged from 23 to 55 years (mean 38.1±9.4) and were similar for both sexes and races. All subjects were susceptible to hepatitis B virus when they joined the study (negative for HBsAg, anti-HBs and anti-HBc [antibody to hepatitis B core antigen]).

Follow-up

We attempted to take a blood specimen from each participant weekly for the first month, monthly thereafter until the third injection at six months and once a month until the anniversary of the initial vaccination. Each specimen was tested for alanine aminotransferase (ALT), HBsAg, anti-HBs and anti-HBc. Compliance was good: all 36 persons received the first two vaccinations and 30 (83.3%) received all three. Failure to complete the vaccination schedule was because of job transfer in five cases and displeasure with the frequent blood specimen taking in one case. Among the 30 persons who finished the injection series an average of 10.8±2.1 (mean ± standard deviation [SD]) follow-up specimens were obtained per person. And for the entire group of 36 subjects the average compliance per visit through month 7 was 85.3%. We were able to get one or more follow-up specimens after month 7 on only 21 persons (58.3%), however, because they left Taiwan.

Vaccine

We used highly purified formalin-inactivated alum-absorbed HBsAg vaccine manufactured by Merck Sharp & Dohme (Lot 751-800C). It was shipped by air on wet ice with a temperature indicator to determine if it had been frozen in transit, after which it was

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
anti-HBc = antibody to hepatitis B core antigen
anti-HBs = antibody to hepatitis B surface antigen
HBsAg = hepatitis B surface antigen
SD = standard deviation

stored at 5°C in the room where it was administered. Three doses of 20 μg were administered intramuscularly; the initial dose was followed by additional doses one and six months later.

Laboratory Studies

ALT determinations were by an optimized UV-kinetic[3] method on an Abbott ABA-50 autoanalyzer. All tests for hepatitis B markers were by radioimmunoassay conducted according to manufacturer's instructions, using kits from Abbott Laboratories, North Chicago, Ill: (1) HBsAg—Ausria II, (2) anti-HBs—Ausab, (3) anti-HBc—Corab. All specimens were tested for ALT and each of the three hepatitis B virus markers. Semiquantitative levels of anti-HBs were expressed as standard deviation units, the number of standard deviations by which the sample count exceeds the mean of the negative controls. It has linear correlation with the amount of antibody except at higher antibody levels where the SD unit calculation gives a falsely low estimate of antibody because of saturation of binding sites.

Results

Adverse Reactions

No reactions occurred. When asked, a few subjects indicated they had mild discomfort at the injection site but most had no complaints. ALT levels remained within the normal range among all vaccinees and there were no conversions to HBsAg or anti-HBc. Two persons had mild fever (37°C, 38°C [99.2°F, 99.8°F]) after the first injection.

Immunogenicity

The response rate was 40% a month following the first dose and 90% a month following the second dose (Figure 1). Among the 30 persons who received all three doses, 28 (93.3%) had antibodies a month following the third dose, which was the time of the peak response. The major effect of the six-month booster, however, was to increase the level of antibody. All 28 responders among the 30 who received three doses had detectable antibody by the time they received the six-

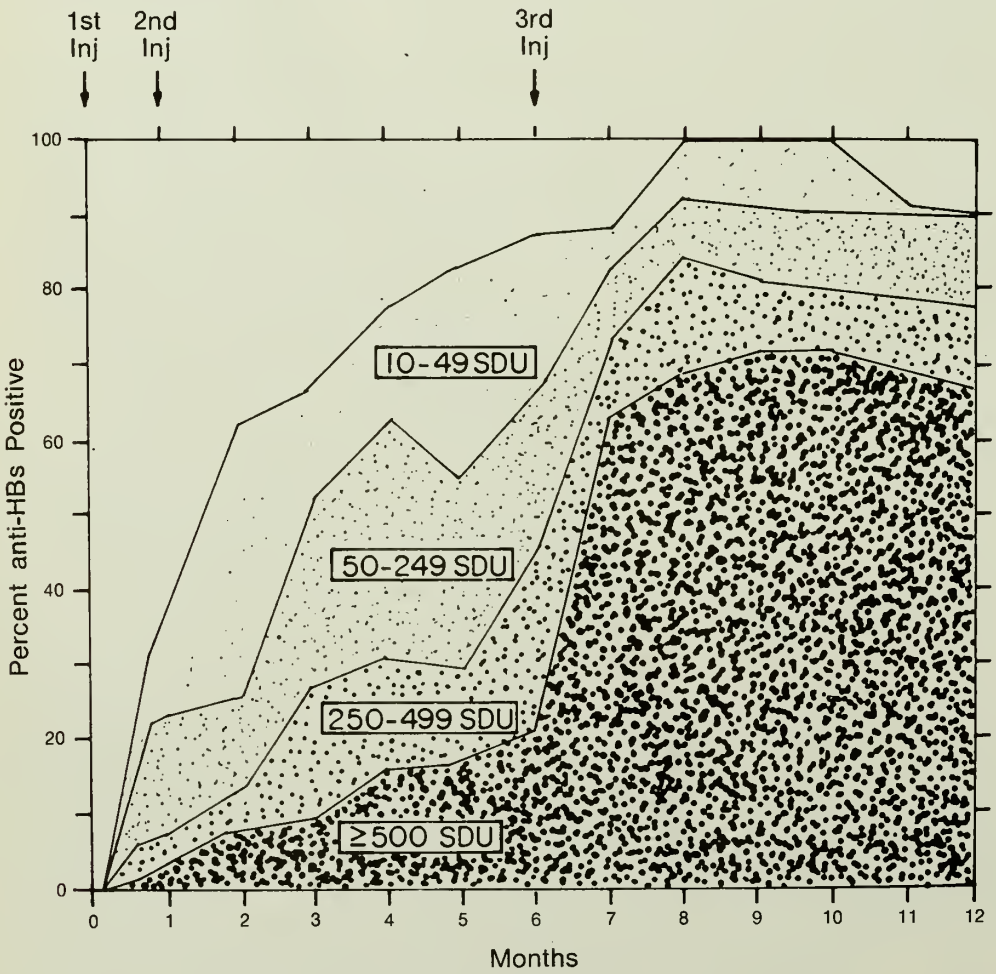

Figure 1.—Immune response of susceptible healthy adults to three 20-μg doses of hepatitis B vaccine (Merck Sharp & Dohme, Heptavax-B). Arrows indicate time of vaccine administration. Ordinate is percent with detectable antibody to hepatitis B surface antigen (anti-HBs) by radioimmunoassay versus months following vaccination. Shaded areas show proportion with varying levels of antibody expressed as standard deviation units (SDU), with larger amounts shown with increasingly heavy shading. Two nonresponders at seven months were not tested at eight to ten months, thus the apparently 100% response rate reflected in the figure.

month booster dose, and all but one of these responded by an increase in amount, usually substantial and rapid. Two persons had no detectable antibody when last tested a month following their third injection. The apparent 100% response in Figure 1 from eight months is misleading because the two nonresponders were not available for testing. Of the six poor responders, only one was Chinese and four were men.

Characteristic Responses to Vaccination

Antibody responses to vaccine fell into four fairly easily separable categories shown in Figure 2: (A) response following the initial vaccine dose, usually in fairly low levels (33.3%), (B) no antibody response following the first injection but a response following the second dose, usually pronounced and often observable a month later (43.3%), (C) weak response often delayed until the six-month booster and response sometimes with later loss of detectable antibody (16.7%) and (D) no response (6.7%).

Discussion

This study shows excellent immunologic responsiveness of most healthy adults to 20 μg of Merck Sharp & Dohme hepatitis B virus vaccine given at zero, one and six months. In about 40% of our subjects antibodies developed within a month of the first injection, rising to about 90% following the second injection and 93% following the third injection.

Our study confirms the value of the six-month booster in substantially increasing anti-HBs titer, which it did in this case by an average of 230%. All but one of those with antibodies following the second dose had a substantial increase in titer following the third dose.

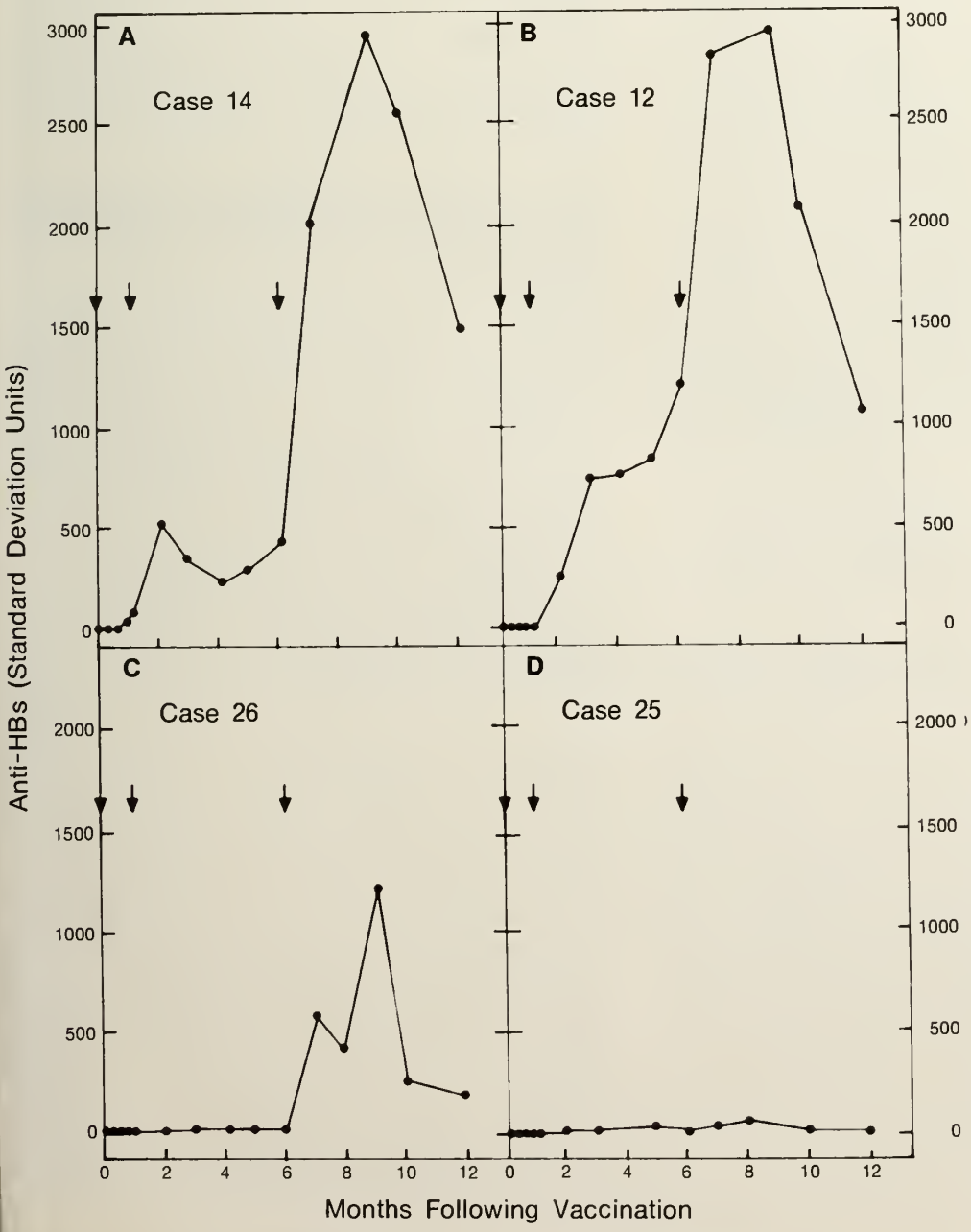

Figure 2.—Characteristic responses of susceptible healthy adults to three doses of hepatitis B vaccine (Merck Sharp & Dohme, Heptavax-B). Arrows indicate time of vaccine administration. Ordinate is level of antibody to hepatitis B surface antigen (anti-HBs) expressed in standard deviation units. Group A had response following initial vaccine dose, usually in fairly low levels (33.3%), Group B had no antibody response following the first injection but a response following the second dose, usually pronounced and often observable a month later (43.3%), Group C had weak response often delayed until the six-month booster and response sometimes with later loss of detectable antibody (16.7%) and Group D had no response (6.7%).

This classical booster response is highly encouraging and implies it can be repeated as needed to maintain antibody titers at levels desired in most persons. Results from efficacy trials suggest that the presence of any level of anti-HBs is usually synonymous with protection.[3-5] No major hepatitis B virus events (excluding conversions to anti-HBc only) occurred among 430 vaccinees in whom anti-HBs developed in the efficacy trial among homosexuals conducted by Szmuness.[3,5]

We observed two nonresponders and four poor responders to vaccination, a poor response rate (23.9%) that was higher than those reported by others.[6,7] Several factors are known to affect antibody response to hepatitis B virus vaccine. These include age, sex and immune competence of vaccinees; dose, frequency and possibly route of vaccine administration. Proper handling of the vaccine is also important. Freezing can cause loss of potency because it disrupts antigen binding to the alum adjuvant and this is considered the likely reason for the lower immunogenicity observed in the efficacy trial in homosexual men conducted by CDC compared with the New York trial of Szmuness.[2,6] Freezing of the vaccine is unlikely in our study because we used a freeze indicator during transit and storage. Furthermore, we did not observe similar problems in simultaneous studies we were conducting in infants and children with the same vaccine.[8-10] Age of the participants in this study is the most likely explanation for our relatively high frequency of poor responders. From infancy through adulthood there is an inverse correlation between age and immunogenicity. Our subjects averaged 10 years older than those in the Szmuness study. In general, men respond slightly less well to vaccination than women and six poor responders were men among 18 male vaccinees compared with two poor responders among the 12 female vaccinees. Impaired immune competence adversely affects immunogenicity but none of our subjects had diseases or medical therapy that would have been likely to alter the immune system.

The results with hepatitis B virus vaccine are highly encouraging. However, the major unknown biologic variable is duration of protection and mean titers in our subjects fell 26% over six months following the third vaccination. Our projections of these values suggest an average extinction about five years following vaccine initiation (unpublished observations). Individual variability, however, is substantial, and some persons lose detectable antibody much more quickly than others. A number of important factors are, however, still unknown and must be considered in relation to strategies for long-term protection with hepatitis B virus vaccine: (1) antibody decay may not be linear, (2) there are probably many subsets of persons with different temporal antibody responses, (3) extinction of detectable antibody may not mean reemergence of susceptibility to infection. This last point is of particular importance; in view of the rapid booster response to vaccine and the long incubation period of hepatitis B, it is quite possible that vaccinated persons will have protection even after detectable antibodies disappear. In fact, in the Szmuness efficacy trial among homosexual men there was evidence of very early protection, supporting this possibility, or even of primary protection during the incubation period.[3,5]

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Oral Rifampin and Trimethoprim/Sulfamethoxazole Therapy in Asymptomatic Carriers of Methicillin-Resistant *Staphylococcus aureus* Infections

RICHARD T. ELLISON III, MD; FRANKLYN N. JUDSON, MD; LYNN C. PETERSON; DAVID L. COHN, MD, *and* JOSEPHINE M. EHRET, *Denver*

During a hospital outbreak of methicillin-resistant Staphylococcus aureus *(MRSA) disease in 30 patients we studied the use of rifampin and trimethoprim/sulfamethoxazole (TMP/SMX) in managing asymptomatic carriers. The outbreak persisted despite control measures including "barrier" precautions, screening cultures, identification of affected persons and rapid hospital discharge of affected patients. The MRSA strain was susceptible to both rifampin and TMP/SMX and in vitro the combination was not antagonistic. Fourteen carriers received a five-day course of rifampin and TMP/SMX given by mouth. Twelve patients were evaluable. Cultures remained persistently positive in four patients, three of whom had foreign bodies that could not be removed. Among the eight with an initial response, two relapsed to the carrier state more than six months after treatment. During the study the outbreak resolved. These data suggest that rifampin and TMP/SMX may decrease the number of MRSA-colonized patients, but may not permanently eradicate the MRSA carrier state.*

(Ellison RT III, Judson FN, Peterson LC, et al: Oral rifampin and trimethoprim/sulfamethoxazole therapy in asymptomatic carriers of methicillin-resistant *Staphylococcus aureus* infections [Clinical Investigation]. West J Med 1984 May; 140:735-740)

Since 1974 methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly recognized as both a nosocomial and a community-acquired pathogen in the United States. By 1981 it had been identified in at least 109 United States hospitals and there were 24 published outbreaks.[1-4] Fortunately, adequate treatment of MRSA infection is usually possible with vancomycin hydrochloride, which appears to have an efficacy comparable to that of β-lactam antibiotics in the treatment of methicillin-sensitive *S aureus* infections.[5,6] However, there has been little success in controlling the spread of MRSA; the infections continue to occur in more than 85% of US hospitals that have recognized the pathogen.[7]

Epidemiologic studies of nosocomial MRSA outbreaks suggest that patients are the major hospital reservoir for the organism. In recent investigations slightly more than 50% of patients who have carried MRSA strains have had clinical infection.[7] The remaining noninfected colonized patients represent a silent reservoir for further nosocomial spread. While three outbreaks have been related to chronic nasal carriage by individual hospital workers, during outbreaks of MRSA infections the prevalence of MRSA carriage in hospital employees with patient care responsibilities has averaged only 2% of those tested; this suggests that this group is only a minor reservoir for the pathogen.[7] MRSA has been cultured from inanimate objects in

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ABBREVIATIONS USED IN TEXT

MIC = minimal inhibitory concentration
MRSA = methicillin-resistant *Staphylococcus aureus*
SMX = sulfamethoxazole
TMP = trimethoprim

hospitals, but such colonization has been implicated neither in spreading the pathogen nor in maintaining the organism in the environment.[1,3,7-9]

Epidemiologic observations of nosocomial MRSA have noted roommate-to-roommate and bed-to-adjacent-bed spread.[7] Transient hand carriage of MRSA strains after contact with colonized or infected patients has been documented and this may be an important mode of patient-to-patient spread.[7-9]

Recommended measures to prevent nosocomial MRSA transmission have included surveillance cultures to identify colonized and infected patients, use of "barrier precautions" to isolate infected or colonized patients and rapid discharge from hospital of infected or colonized patients when it is medically feasible.[10]

Ward and his associates reported that a regimen effective in eradicating colonization with MRSA was (1) topical bacitracin ointment three times a day for five days, (2) hexachlorophene baths during the initial two days and (3) rifampin (300 mg) given by mouth twice a day for five days with or without trimethoprim/sulfamethoxazole (TMP/SMX) 80 mg/400 mg twice a day for five days.[11] In this study we report our in vivo and in vitro observations on the efficacy of combined oral rifampin and TMP/SMX therapy alone in eradicating colonization with MRSA during an apparently typical outbreak at a city hospital.

Patients and Methods

Denver General Hospital is a 300-bed facility serving mainly indigent patients in the Denver metropolitan area. The hospital has 56 medical beds, 126 surgical beds, 52 pediatric beds, 35 obstetric-gynecologic beds and 60 psychiatric beds. There are four intensive care units (one medical, one surgical, one combined medical-neurosurgical and one pediatric). There were 16,294 hospital admissions in 1982. An outbreak of MRSA disease was first recognized in August 1981 and this report includes all patients and personnel subsequently identified who had one or more cultures positive for MRSA.

Methicillin-resistant *Staphylococcus aureus* cases were identified through review of all clinical microbiology laboratory isolates and by surveillance cultures carried out on personnel and patients having direct contact with known cases. Cultures of specimens from anterior nares, wounds and other potentially infected sites were done. Cases were classified as either infection or colonization on the basis of history, physical examination, laboratory studies and clinical course.

Bacteriologic Methods

MRSA isolates were identified by compatible colony morphology and Gram's stain, a positive coagulase test and resistance to oxacillin by the disc diffusion technique of Kirby-Bauer.[12,13] Surveillance cultures were done on mannitol salt agar. Bacteriophage typing was carried out on an isolate from each case by the Centers for Disease Control, Atlanta.

Antimicrobial Susceptibility Testing

Isolates from each case were stored at −70°C in trypticase soy broth with 15% glycerol. Rifampin diagnostic powder was obtained from CIBA Pharmaceutical Co (Summit, New Jersey) and sulfamethoxazole and trimethoprim from Hoffmann-LaRoche, Inc (Nutley, New Jersey). Minimal inhibitory concentrations (MIC) to rifampin, TMP, SMX and combinations of rifampin, TMP, TMP/SMX and rifampin/TMP/SMX were determined by an agar dilution method using Sensitest agar (Oxoid, Columbia, Maryland) containing 5% lysed horse erythrocytes. Inocula of 0.003 ml were delivered by multipoint inoculator using overnight cultures in Mueller-Hinton broth diluted to an inoculum of 100,000 colony-forming units per ml.[14,15] Plates were incubated for 24 hours at 35°C. The MIC was defined as the lowest concentration of antibiotic at which no growth occurred. Activity of rifampin was tested with serial twofold dilutions from 25 to 0.003 μg per ml, TMP with twofold dilutions from 1.6 to 0.003 μg per ml and SMX with twofold dilutions from 31.2 to 0.03 μg per ml.

Time-kill curves with rifampin, TMP/SMX and rifampin/TMP/SMX were carried out with one isolate of MRSA. Studies with selected antibiotic concentrations were done using 100,000 colony-forming units per ml of MRSA in Sensitest broth (Oxoid) containing 5% horse erythrocytes. Aliquots were removed at 0, 4, 24 and 48 hours and incubated overnight at 35°C.

Control Measures

All patients identified as being either colonized or infected with MRSA were placed in private rooms with "gown-and-glove precautions." The responsible physicians were encouraged to discharge the patients as soon as it was medically indicated and their charts were prominently labeled for rapid recognition during subsequent clinic visits or hospital admissions. The one employee colonized with MRSA who remained at the hospital was removed from patient care while colonized.

After November 1981 the patients and employee colonized with MRSA were treated with rifampin, 600 mg given twice a day by mouth, and TMP/SMX, 160 mg/800 mg given twice a day by mouth, for five days. Any removable foreign bodies (urethral catheters, endotracheal tubes, intravenous catheters) were replaced on the third day of therapy. Follow-up cultures of all colonized sites were done in each treated patient.

Results

Between August 1981 and May 1982 a total of 29 patients and one employee were identified as being

colonized or infected with MRSA (Figure 1). No new cases were identified in the subsequent six months and, for the purpose of this study, the outbreak was considered to be "controlled." In all, 28 of the patients and the one employee were found to have bacteriophage type 53/83A/85+. The remaining patient had MRSA of indeterminate bacteriophage type isolated from a foot ulcer on his initial visit to the hospital and was felt to have a community-acquired organism that was not part of the outbreak. This outbreak was epidemiologically typical of nosocomial outbreaks of MRSA reported previously.[1-7]

The characteristics of the cases were similar to those described by others (Table 1). These patients had very prolonged hospital stays and tended to acquire the MRSA late in their hospital course after receiving numerous antibiotics. Of the patients, 6 were infected and 22 were colonized. Two infected patients (33%) died of MRSA infection while six colonized patients (27%) had unrelated deaths. Of the first 12 cases, 10 occurred on one general surgical service and in the other 2 early cases the patients were in the same hospital unit as patients from this service. MRSA subsequently became endemic in the surgical and joint medical-neurosurgical intensive care units and then involved patients on other surgical services. Transmission of the organism most commonly occurred from roommate to roommate, apparently on the hands of personnel. During the outbreak ten colonized patients were readmitted to either this hospital or another facility, although no secondary cases arising from contact with these patients were identified. Two patients had their first culture for MRSA noted immediately on readmission following a hospital admission during the outbreak period. One of these two admissions occurred in a hospital in another state.

Surveillance cultures were carried out on 87 hospital personnel who had patient contact and 23% were found to be colonized with methicillin-sensitive *S aureus*. The outbreak strain of MRSA was found in cultures from two of the personnel, one who had persistently positive cultures from eczematous skin and a second who left the facility before follow-up cultures could be done to ascertain that they were persistently positive. Neither of these employees was present at the onset of the outbreak, nor could they be directly implicated in the spread of the pathogen.

The MRSA strain had a consistent antibiogram during the outbreak with disc diffusion tests showing sensitivity to gentamicin, amikacin and vancomycin and resistance to penicillin, oxacillin, tobramycin, clindamycin, erythromycin and tetracycline. Fifteen of the initial isolates were tested for TMP, SMX and rifampin MICs. All were sensitive to TMP (0.2 μg per ml) and SMX (3.9 to 7.8 μg per ml). Whereas all were sensitive to rifampin, 12 of the isolates had an MIC of 0.003 μg per ml or less and three obtained late in the outbreak had an MIC of 0.1 μg per ml. Antagonism between rifampin and TMP/SMX was not found in ten strains tested by a checkerboard technique.

From December 1981 through May 1982 there were 14 MRSA-colonized patients and personnel who received 17 courses of an oral regimen of rifampin and TMP/SMX (Table 2). Two patients were not available for follow-up; one died of his underlying illness one day after completion of the regimen and the other was discharged from hospital and did not return. Of the remaining 12 patients, 4 had positive cultures for MRSA within ten days of the end of therapy. Three were retreated with the five-day regimen and two again had positive cultures within three days. One had nasal MRSA colonization and multiple facial bone fractures

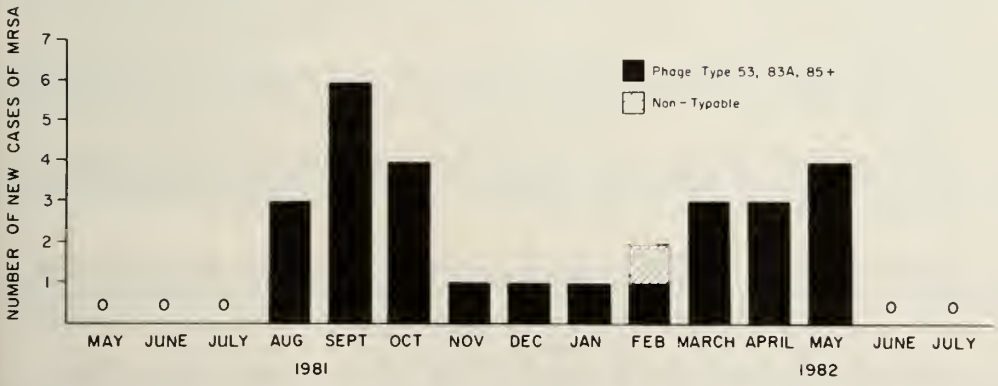

Figure 1.—New cases of methicillin-resistant **Staphylococcus aureus** (MRSA) colonization or infection, August 1981 through May 1982.

TABLE 1.—*Characteristics of Patients Colonized or Infected With Methicillin-Resistant* Staphylococcus aureus *53/83A/85+*

	Mean ± Standard Error	*Range*
Age (years)	51.8 ± 4.1	20 to 86
Total duration of hospital stay (days)	72.1 ± 10.4	6 to 196
Interval from admission to first isolate (days)	38.3 ± 5.1	6 to 89
Number of different antibiotics received before first isolate	4.2 ± 0.1	0 to 9
Number of patients colonized	22	
Number of patients infected	6	

stabilized by interosseus wires and the other persistent sputum colonization in association with obstructing squamous cell lung carcinoma at the carina. Among eight patients with negative initial follow-up cultures, two had negative cultures for MRSA within the first month after treatment but then had cultures positive for the epidemic strain six and nine months after treatment. Neither of these patients was known to have had new contact with MRSA. In none of the remaining six patients could new cultures be done more than a month after the completion of the rifampin/TMP/SMX therapy, four patients had died and two were lost to follow-up.

No patient had an adverse reaction to the three-drug regimen. However, the one patient in whom the therapy failed and who was not re-treated with the five-day regimen received the three drugs inadvertently for 18 days. In this patient an asymptomatic aminotransaminase elevation developed that resolved and then recurred after a single dose of rifampin.

Paired MRSA isolates before and after therapy were available in three patients in whom the therapy failed. The patient who had interosseus wires in place was treated twice and there was a successive rise in rifampin MIC from 0.003 or less to 0.1 to 0.8 μg per ml although there was no change in TMP or SMX susceptibility. In the patient who received prolonged therapy there was a rise in rifampin MIC from 0.003 or less to more than 25 μg per ml, again without changes in TMP or SMX susceptibility.

Time-kill curves of the activity of rifampin, TMP/SMX and rifampin/TMP/SMX were carried out with the initial isolate from the patient with interosseus wires in place in whom therapy failed. The isolate was tested in the presence of presumed serum concentrations of the antibiotics (rifampin 1 μg per ml, TMP 1 μg per ml and SMX 20 μg per ml) and rapid killing occurred with all combinations (Figure 2). The isolate was then tested using concentrations of antibiotics that were twice the in vitro MICs, 0.006 μg per ml for rifampin and 0.5/1.0 μg per ml for TMP/SMX. At these antibiotic concentrations not only was rapid resistance to rifampin demonstrated, but TMP/SMX did not prevent the emergence of rifampin resistance (Figure 3).

Discussion

Optimal management of a persistent carrier of *S aureus* has yet to be defined. Studies of the natural history of nasal *S aureus* carriage show that multiple staphylococcal strains may be present concurrently and fluctuate as to relative numbers.[16] Predominant strains can persist for as long as 21 years.[16] Attempts to control nasal staphylococcal carriage with topical antibiotic ointments have succeeded in decreasing the numbers of staphylococci present, but not in their eradication.[17] The replacement of a pathogenic staphylococcal strain with a supposedly nonpathogenic strain, *S aureus* 502A, has been found to aid in controlling nosocomial outbreaks and recurrent furunculosis, but its usefulness has been limited by both the need for repetitive instil-

TABLE 2.—*Outcome of Oral Rifampin/Trimethoprim/Sulfamethoxazole Therapy in 13 Patients and One Employee Colonized With Methicillin-Resistant* Staphylococcus aureus *(MRSA)*

Patient Number	*Underlying Illness*	*Colonization Site(s)*	*Posttherapy Culture Results* (day of culture)*	*Comment(s)*
2	Lung carcinoma	Sputum	4+; re-treated, 1+, 3+, 6+	Bronchial obstruction with carcinoma
7	Cholangiocarcinoma	Nose, bile	1−, 11−, 33−	Biliary drainage tube
10	Abdominal gunshot wound	Sputum, abdominal wound	15−, 35−	Concurrent vancomycin therapy for MRSA bacteremia
14	Basilar skull fracture	Sputum	1−, 2−, 3−, 4−	Tracheostomy
15	Pelvic fracture	Abdominal wound	2−, 6−, 17−, 29−, 60−, 274+	Recurrent MRSA noted 9 months after therapy
17	Cervical spine gunshot wound, quadriplegia	Sputum	6−, 10−	
18	Peripheral vascular disease	Abdominal wound	2−, 4−	Unrelated death 6 days after treatment
19	Automobile accident, facial bone fractures	Nose, sputum, facial wound	2+, 5+, 25+, 27+, 40+; re-treated, 3+, 57+, 83+	Interosseus wire fixation of fractures
20	Subdural hematoma	Nose, sputum, ankle decubitus	Not cultured	Unrelated death 1 day after treatment
22	Lung carcinoma	Nose, sputum, axilla, groin	2−, 8−	
23	Hidradenitis suppurativa	Perineal skin graft	3−, 10+; re-treated, 3−, 61−	
24	Subdural hematoma	Nose, sputum	1+, 6+, 26+	Tracheostomy, not re-treated with 5-day regimen
25	Abdominal wall abscess	Abdominal wound	Not cultured	Discharged from hospital without follow-up cultures
28	Employee	Eczematous hand lesions	2−, 140+, 154+	Recurrent MRSA noted 6 months after therapy

*+ indicates isolation of MRSA, − indicates no growth of MRSA (for example, 4− indicates no growth of MRSA on cultures obtained on fourth day after therapy).

lations to suppress the pathogenic strains and the finding that this strain is itself occasionally pathogenic.[18-20] Studies in volunteers have shown that macrolide antibiotics given by mouth can decrease the intensity of nasal staphylococcal carriage and that rifampin given by mouth can temporarily eliminate it, but controlled studies of their clinical utility in persistent staphylococcal carriage have not been done.[21-23] Further, the use of rifampin as a single agent has not been advocated because of concern over the possibility that rifampin resistance would rapidly emerge.

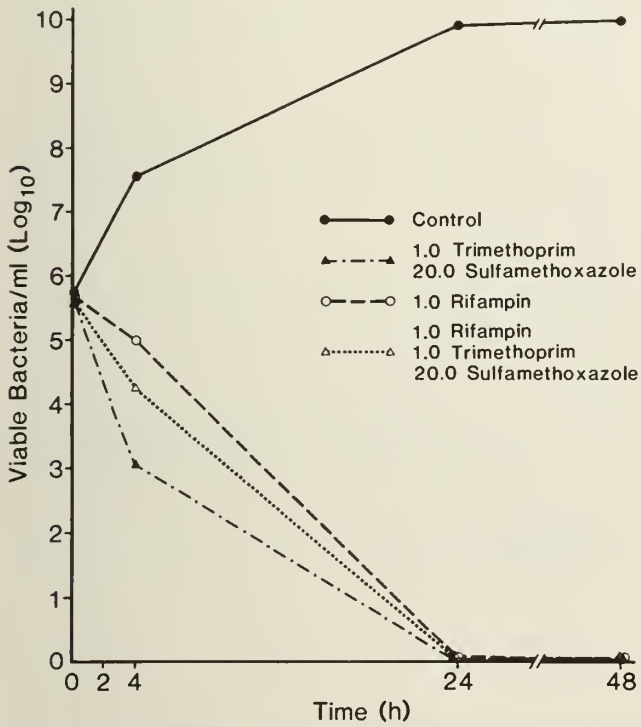

Figure 2.—Activity of rifampin, trimethoprim/sulfamethoxazole and rifampin/trimethoprim/sulfamethoxazole against an isolate of methicillin-resistant *Staphylococcus aureus* at expected serum concentration of the antibiotics.

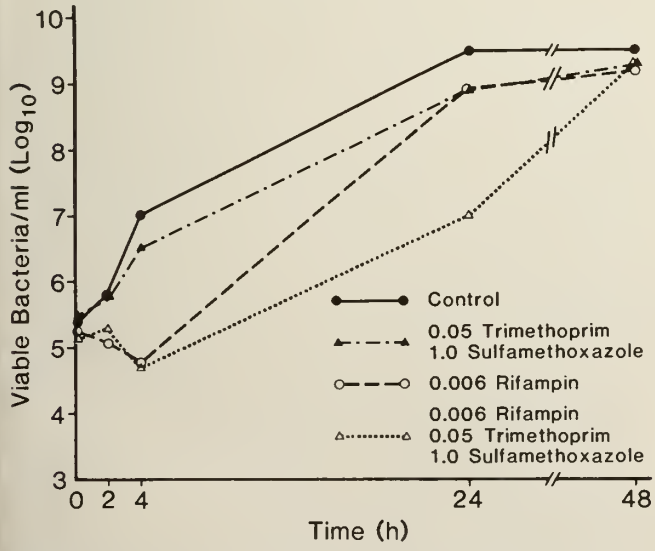

Figure 3.—Activity of rifampin, trimethoprim/sulfamethoxazole and rifampin/trimethoprim/sulfamethoxazole against an isolate of methicillin-resistant *Staphylococcus aureus* at twice the in vitro minimal inhibitory concentration of the antibiotics.

Ward and co-workers reported that a regimen of topical bacitracin ointment, hexachlorophene baths and rifampin by mouth with or without TMP/SMX was effective in eradicating MRSA colonization.[11] They evaluated the cases of 16 patients treated with rifampin with an 81% eradication rate and 26 patients treated with rifampin and TMP/SMX with 88% eradication. Follow-up cultures were obtained between the 2nd and 40th week after treatment and the number of follow-up cultures obtained was not noted. Rifampin resistance was found in two of three patients in whom therapy without TMP/SMX failed but in none of three who received combined therapy.

Based on this work we undertook an evaluation of combination oral therapy with rifampin and TMP/SMX in asymptomatic carriers of MRSA at a time when our hospital was undergoing an outbreak similar to those previously reported. In our institution we found that in vitro the epidemic strain was sensitive to all three antibiotics by agar diffusion testing, without antagonism noted. Unfortunately, initial suppression of MRSA was found in only 8 of 12 initial trials and 1 of 3 repeat trials. Clinical failure was partially predicted by the presence of a foreign body at the colonized site. With a five-day regimen, drug toxicity was not seen; however, drug-resistant isolates did occur when the protocol failed or was prolonged. Time-kill curves suggest that while TMP/SMX could prevent the development of rifampin resistance at serum concentrations, at lower antibiotic concentrations, which might be present at poorly vascularized sites, TMP/SMX did not prevent rifampin resistance in the epidemic strain tested.

Additionally, following early suppression of MRSA, there was in two patients asymptomatic recolonization with the epidemic strain without obvious cause. Relapse with resistant organisms did not occur in these patients. This suggests that a prolonged carrier state developed following colonization with MRSA and that this state was refractory to the oral regimen we used. It had not been anticipated that relapse could occur after the first month and, as most of our patients did not have prolonged follow-up, we could not establish the incidence of such persistence. Consequently, we feel that treatment with this rifampin/TMP/SMX regimen cannot be presumed to reliably eradicate the carrier state. Our results differ from those reported previously when this combination was used in conjunction with bacitracin ointment and hexachlorophene baths. The difference may relate to the lack of these topical agents in our protocol, more prolonged follow-up in our study or to the culturing techniques of a zealous infection control nurse who vigorously swabbed the skin surfaces of the patients on follow-up.

It is possible that the inability of oral antibiotic therapy to completely eradicate carriage may not preclude its usefulness in controlling nosocomial MRSA

outbreaks. We speculate that a transient decrease in MRSA colonization may have accounted for the fact that we did not recognize any secondary cases arising from contact with a patient treated with this protocol.

In this study we showed that rifampin and TMP/SMX have in vitro activity against MRSA. Clinically five days of combined therapy had only limited success in eradicating carriage of MRSA during a typical outbreak, but during our evaluation of the regimen this outbreak of MRSA infections resolved. This therapy should undergo further controlled investigations to establish its usefulness in the management of nosocomial MRSA outbreaks.

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Outpatient Theophylline Determinations

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The indications and usefulness of outpatient serum theophylline determinations were prospectively evaluated by doing 151 of these studies in 137 consecutive cases of chronic obstructive pulmonary disease. We found that evaluations were done for the following three groups of indications: group A, worsening bronchospasm; group B, stable asymptomatic cases, and group C, symptoms suggesting theophylline toxicity. When the three clinical groups were compared for frequency of nontherapeutic values, only an increased frequency of subtherapeutic values in patients with bronchospasm (group A) was significant (P<.01). Increasing the dosage up to 15 mg per kg of body weight a day while theophylline determinations are pending appears to be safe in this group of patients. Toxic symptoms were rarely associated with concentrations greater than 20 μg per ml (3/13) and infrequently occurred in patients with concentrations greater than 20 μg per ml (3/29). Nontherapeutic theophylline values did not always result in an adjustment of theophylline dosage. This was influenced by a correlation of symptoms, timing of the theophylline determination and the use of other bronchodilators.

(Knodel AR, Covelli HD, Beekman JF: Outpatient theophylline determinations [Clinical Investigation]. West J Med 1984 May; 140:741-744)

Serum theophylline determinations are often recommended to ensure optimum effect and avoid complications.[1-3] In patients who are in hospital, these determinations are readily available and of proved clinical value.[1,4] However, in an outpatient setting where access to a laboratory may be limited and therapy is often long-term, the role of serum theophylline determinations is less clear. Guidelines for dosage and serum concentration determinations in the initiation and maintenance of outpatient theophylline therapy have been proposed.[2,5] These recommendations may not be practical for each person, however, because of intrapatient variability in theophylline kinetics,[6-8] an incomplete patient data base and concern about making therapeutic decisions on the basis of a single test.

By noting the indications for theophylline determinations and the modification of therapy resulting from these values, we evaluated why theophylline concentrations were determined, their correlation with symptoms and how they influenced management.

Patients and Methods

In all, 151 theophylline determinations were done in 137 patients. All patients had chronic airflow obstruction (forced expiratory volume in one second [FEV_1] to forced vital capacity, less than 75%) and showed at least a 15% improvement in FEV_1 after receiving an aerosolized sympathomimetic bronchodilator. Patients' ages were from 38 years to 89 years, with a mean of 62.3. Ten patients had associated congestive heart failure and three had minor abnormalities of liver function. Of the 137 patients, 25 were still smoking cigarettes. A single determination was done in 122 patients. Two serum concentrations were obtained in 13 patients and three in two patients.

The theophylline determinations were requested by

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TABLE 1.—*Theophylline Dosage and Serum Values According to Clinical Groups**

	Dose (mg/kg/d)	Serum Concentrations μg/ml: Peak Determination† N=47	Trough Determination‡ N=104	Average
Group A				
Poorly controlled or worsening bronchospasm	14.6±5.9	15.0±10.1	14.1±8.6	14.3±9.1
Group B				
Stable	14.4±4.2	16.2±10.4	13.9±5.6	14.5±6.9
Group C				
Symptoms of toxic reaction	17.8±5.4§	16.2± 6.7	13.5±6.5	14.5±6.6

*Mean ± standard deviation.
†Obtained 1.8±0.5 hours post dose.
‡Obtained 4.8±1.1 hours post dose.
§$P<.05$ compared with groups A and B.

five pulmonary staff and six house-staff physicians over a four-month period beginning in January 1982. The physicians were informed on a monthly basis that all theophylline determinations and subsequent dosage modifications were to be reviewed. They were instructed to note theophylline dosage, frequency of dosage and timing of the test with respect to dosage and to have assurances of compliance with medications before obtaining plasma theophylline concentrations. The patients' charts were then reviewed after the physicians had completed their evaluation and treatment. The indications for the measurement and action taken by physicians on the basis of the test results were noted. When a patient had not been taking a theophylline preparation for at least 72 hours or could not give an assurance of compliance, that patient was excluded from the study. Theophylline determinations were run twice a day in our laboratory: 10 AM and 4 PM. Any value greater than 20 μg per ml was immediately reported back to the clinic. All other values were reported to the ordering physician within one to two working days. In all cases, the laboratory report required initialing by an attending physician before a chart was reviewed by an investigator.

The indications for theophylline determinations were divided into the following three categories: (1) (group A) poorly controlled or worsening bronchospasm; based on a patient's complaints of increasing dyspnea, cough or wheezing; prolonged expiration or wheezing noted on chest auscultation, and decreased flow rates recorded by spirometry; (2) (group B) routine monitoring in patients with stable symptoms and (3) (group C) a toxic reaction based on a patient's complaints or symptoms of nausea, vomiting, abdominal cramps, diarrhea, arrhythmias, fever, agitation or seizures.

In all cases, the patients were taking rapidly acting theophylline preparations. The amount of theophylline administered was calculated from the theophylline content as a percent of dry weight of compound given: 100% for anhydrous theophylline, 81% for aminophylline (theophylline with ethylenediamine) and 65% for oxtriphylline (theophylline with choline). Seven patients were taking three doses a day, eight patients five doses a day and the rest four doses a day. Peak-and-trough determinations were those obtained one to two hours and four to six hours after dosing, respectively. Four patients on three-times-a-day dosing had trough determinations. In all cases, this was obtained 5.5 to 6.5 hours after dosing.

Theophylline concentrations were determined by the enzyme immunoassay. The coefficient of variation for the assay is 5% in our laboratory. Values between 10 and 20 μg per ml were considered therapeutic.[9,10]

Student's *t* test was used to evaluate the significant differences between means. Z values were calculated to test for significant differences between two proportions.

Results

Most serum theophylline values were obtained from symptomatic patients. A total of 79 determinations (52%) were done in patients with poorly controlled bronchospasm (group A) and 13 (9%) in patients with symptoms suggestive of theophylline toxicity (group C). The remaining 59 (39%) determinations were from well-controlled, asymptomatic patients (group B). The dosage and values for the three clinical groups are shown in Table 1.

In all, 77 (51%) of the theophylline levels were considered outside the therapeutic range, with nearly twice as many subtherapeutic as "toxic" levels (Table 2). Symptomatic patients (groups A and C) were more likely to have a nontherapeutic theophylline level. When the three clinical groups were compared for frequency of "toxic" levels, there was no significant difference. However, there were significantly ($P<.01$) more patients with subtherapeutic levels of theophylline who had poorly controlled bronchospasm—31/79 (39%)—than those who did not, 17/72 (24%).

Of the 16 values obtained in patients who had toxic symptoms (Table 3), only three were higher than 20 μg per ml. These three represented 10% (3/29) of the total number of levels higher than 20 μg per ml.

In all, 60% of patients with nontherapeutic theophylline concentrations had no alterations in their dosage. Physicians were no more likely to decrease the theophylline dose in a patient with a "toxic" concentration (12/29) than to increase it in a patient with a subtherapeutic one (18/48) ($P>.05$). However, patients whose symptoms correlated with their values were more likely to have a dosage modification.

Of 31 group A patients with concentrations lower than 10 μg per ml, 16 had a dosage increase and two out of three group C patients with values greater than 20 μg per ml and symptoms had a dosage decrease. This compared with a dosage increase in only 2/17 group B and C patients with concentrations of less than 10 μg per ml and a dosage decrease in 10/26 group A and B patients with concentrations greater than 20 μg per ml (18/34 [53%] versus 12/43 [28%], $P<.01$) (Table 4). Out of the 15 group A patients who did not get an increase in theophylline dosage despite a subtherapeutic value, five were given steroids and three oral β_2-agonists.

Discussion

Theophyllines are effective bronchodilators that have a narrow therapeutic range. Poor patient compliance, variability in metabolism during prolonged therapy and intermittent dosing may complicate its outpatient use and justify theophylline determinations.[6-8] Our study showed that a patient's clinical presentation influences selection for determination and subsequent dosage adjustment. We found that symptoms often do not correlate with subtherapeutic or toxic values and obtaining theophylline concentrations will prevent inappropriate dosing changes.

Jacobs and co-workers[1] reviewed 75 serum theophylline determinations obtained on 47 in-hospital patients who had obstructive lung disease. He found 31 (41%) toxic and 11 (15%) subtherapeutic values for a 56% incidence of nontherapeutic values. In a study of 83 patients receiving 200 or 300 mg of theophylline orally every six hours, Jenne and associates[9] found 13 patients (16%) with toxic and 36 (43%) with subtherapeutic values. In our study, 51% of the serum determinations were outside of the standard therapeutic limit. In contrast to Jacobs's but consistent with Jenne's study, subtherapeutic values were more than twice as frequent as toxic values. The high incidence of nontherapeutic values despite a mean dose of 14.8 mg per kg of body weight a day and a mean serum concentration of 14.4 μg per ml emphasizes the pronounced intrapatient variability in theophylline metabolism and supports the use of theophylline determinations in an outpatient setting.[2,11]

In our study, 61% of all determinations were obtained in patients with symptoms of either worsening bronchospasm or theophylline toxicity. Patients with worsening bronchospasm had a statistically significant increased frequency of subtherapeutic values compared with the asymptomatic and symptomatically toxic patients. It would have been unsafe, however, to raise the theophylline dose in all patients who had bronchospasm, as 20% had concentrations greater than 20 μg per ml. On the other hand, no patient with bronchospasm receiving less than 15 mg per kg a day had a value greater than 20 μg per ml, suggesting an increase of theophylline dosage up to this level would be associated with few toxic reactions. It should be noted that this group included four patients who had congestive heart failure but none who had hepatic disease.

Toxic symptoms poorly correlated with serum concentrations greater than 20 μg per ml. Only 23% (3/13) of patients with toxic symptoms had values greater than 20 μg per ml, whereas 10% (3/29) of patients with concentrations greater than 20 μg per ml had toxic symptoms. In contrast, 11/14 (79%) of values greater than 25 μg per ml were associated

TABLE 2.—*Frequency of Nontherapeutic Theophylline Values According to Clinical Indication for Determination*

	Nontherapeutic Serum Theophylline Concentration			
	<10 μg/ml		*>20 μg/ml*	
	Number	*(Percent)*	*Number*	*(Percent)*
Group A				
Poorly controlled or worsening bronchospasm (79 determinations)	31	(39)	16	(20)
Group B				
Stable (59 determinations)	14	(24)	10	(17)
Group C				
Symptoms of toxic reaction (13 determinations)	3	(23)	3	(23)
TOTAL (151 determinations)	48	(32)	29	(19)

TABLE 3.—*Symptoms Possibly Related to Theophylline Toxicity*

Symptoms	*Number of Patients*
Anorexia, nausea, vomiting	9*
Insomnia, restlessness	5
Tachyarrhythmias	2†

*Two patients had serum theophylline concentrations of >20 μg per ml.
†One patient had a serum theophylline concentration of >20 μg per ml.

TABLE 4.—*Physician Response to Nontherapeutic Theophylline Values According to Clinical Groups*

	Frequency of Subtherapeutic Concentrations (<10 μg/ml) Resulting in Dose Increase No./No. Tested (Percent)		*Frequency of Toxic Concentrations (>20 μg/ml) Resulting in Dose Reduction No./No. Tested (Percent)*	
Group A				
Poorly controlled or worsening bronchospasm	16/31	(52)	6/16	(38)
Group B				
Stable	2/14	(14)	4/10	(40)
Group C				
Symptoms of toxic reaction	0/3	(0)	2/3	(67)

with toxic symptoms in Jacobs's study.[1] Jenne and colleagues[9] found that 7/13 patients with concentrations greater than 20 μg per ml had definite or possible toxic symptoms. Most of Jacobs's patients were receiving a continuous infusion of theophylline and all theophylline values in Jenne's study were trough determinations. Nearly half of our toxic values were peak determinations, with a decrease in concentrations to be expected during the dosing interval.

In our study, only 39% (30/77) of nontherapeutic values resulted in dosage modification. However, not reducing dosage when peak concentrations were between 20 and 30 μg per ml may be acceptable. Rangsithienchai and Newcomb[2] frequently noted peak theophylline concentrations of greater than 28 μg per ml, with trough of less than 20 μg per ml. Many of these patients specifically denied having symptoms of toxic effect. Piafsky and Ogilvie[3] found a mean difference of 8 μg per ml between maximum and minimum theophylline concentrations in adults taking medication by mouth. A peak value between 20 and 30 μg per ml likely results in a trough between 10 and 20 μg per ml. Because bronchodilation correlates with serum concentrations,[4,9] a peak value of higher than 20 would be acceptable to maintain maximum bronchodilation throughout the dosage interval, especially in patients with poorly controlled bronchospasm. Similarly, a trough value of 5 to 10 μg per ml in a stable patient would be acceptable because some bronchodilation occurs at a concentration of 5 μg per ml[4] and the peak value would probably be between 10 and 15 μg per ml.

An increase in the theophylline dosage would seem warranted in patients with subtherapeutic theophylline concentrations and worsening bronchospasm. Surprisingly, no change in treatment was made in 15/31 patients in our series with this clinical constellation. We speculate that there are two reasons for this. First, most of those patients without changes in theophylline dosage had an addition of steroids or oral β_2-agonists. Second, the rest improved over the ensuing 24 to 48 hours while the theophylline test results were pending.

In our investigation, we evaluated the clinical correlation of theophylline determinations in outpatients. We found that increasing theophylline dosage up to 15 mg per kg a day in patients with bronchospasm can be done safely while serum values are pending. Peak theophylline concentrations of 20 to 25 μg per ml in patients with poorly controlled bronchospasm without toxic symptoms appear acceptable. There is poor correlation between serum concentrations and minor toxic symptoms and, therefore, peak determinations should be obtained before reducing dosages on clinical grounds alone. In general, outpatient serum theophylline concentrations should be interpreted in the context of clinical findings, the timing of the determination with respect to the dosage and the absolute theophylline level.

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Original Clinical Articles

Myocardial Revascularization for Patients With an Ejection Fraction of 0.2 or Less

12 Years' Results

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From 1969 through December 31, 1981, a total of 232 patients with an ejection fraction of 0.2 or less (normal 0.67) had myocardial revascularization. The in-hospital mortality in these patients decreased from 25 deaths in 82 patients (30%) from 1969 through 1972 to 10 deaths in 150 patients (7%) from 1973 through December 31, 1981. There was a 24% five-year survival for patients in congestive heart failure at the time of operation, a 40% survival at five years for patients successfully treated for failure before operation and a 60% five-year survival for those patients who had never been in failure. These results would appear to be better than those with cardiac transplantation, with neither the restrictions for operation nor the long-term immunotherapy required with cardiac transplantation.

(Zubiate P, Kay JH, Dunne EF: Myocardial revascularization for patients with an ejection fraction of 0.2 or less—12 years' results. West J Med 1984 May; 140:745-749)

Patients with an ejection fraction of 0.2 or less (normal 0.67) have been considered inoperable and, if operated on, it was thought their clinical state would not be improved or longevity enhanced. In contradistinction to this, we have thought that patients who had an ejection fraction of 0.2 or less could be operated on with a reasonable mortality rate and that their clinical state and longevity could be improved. The first patient who had an ejection fraction of 0.2 or less was operated on in August 1969. From then through December 31, 1981, 232 patients with an ejection fraction of 0.2 or less have had myocardial revascularization. In the following report we describe the 12-year experience with these patients. Patients who had a ventricular aneurysm were excluded from this series, as were patients who had valvular heart disease. The group of patients reported are those with grossly hypokinetic hearts. Some areas of the heart contracted slightly better than others, but the overall contraction was poor.

Clinical Findings

In all, 61 (26%) of the patients were 50 years of age or younger and 171 (74%) were older than 50 years at the time of operation. The oldest patient was 76 and the youngest was 27 years of age. The median age was 57 years. There were 150 (65%) patients in class III of the New York Heart Association functional classification and 82 (35%) in class IV, judged by symptoms other than angina. Eleven patients (5%) gave a history of three or more myocardial infarcts, 29 (13%) had two infarcts, 168 (72%) had one infarct and 24 (10%) patients did not recall having had an infarct, nor was a history of infarction obtained.

From August 1969 through December 1973, forward angiocardiography was done to determine the function of the left ventricle. The reasons for this were to evaluate the presence and amount of tricuspid insufficiency, to determine the transit time from right to left side, to determine the amount of left atrial contraction and left atrial kick and to produce fewer ventricular premature contractions. Of 102 patients, 62 (61%) had forward angiocardiography and 40 (39%) had left ventriculography during this period. From January 1974 through December 31, 1981, 121 of 130 patients (93%) were studied by left ventriculography and only 9 (7%) by forward angiocardiography

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alone. The ejection fraction of the left ventricle was measured by the area-length method as modified for single-plane right anterior oblique cineangiocardiography using a mechanical planimeter.[1] The ventricular volume was calculated as follows: ventricular volume equals $8/3\pi \times A^2/L$ where A is the planimetered area in 30 degrees of right anterior oblique position and L is the longest axis of the same silhouette. There has been no change in the method of studying or calculating a patient's ejection fraction since beginning this study in 1969.

The left ventricular end-diastolic pressure was measured preoperatively in 169 of the 232 patients and varied from less than 10 to as high as 53 mm of mercury. Preoperatively, the systolic pulmonary artery pressure varied from a high of 80 to a low of 15 mm of mercury with a mean of 46 in the 104 patients in whom it was measured, and the pulmonary artery diastolic pressure varied from 45 to 2 mm of mercury in these same 104 patients.

If a patient was in failure before operation, that patient was admitted to hospital two to four days early to attain an optimal condition before the surgical procedure. A patient in failure had rest dyspnea, orthopnea, hepatomegaly, ascites, edema, rales and gallop rhythm. In some patients these symptoms and signs cleared with bed rest, diuretics and fluid restriction in hospital. In other patients none of these signs or symptoms were exhibited before operation, despite an ejection fraction of 0.2 or less.

The operative technique used has been described previously by Zubiate, Kay and Mendez[2] and, briefly, consisted of opening the chest through a median sternotomy incision, measuring the pulmonary artery pressure and left atrial pressure and withdrawing one or two units of blood through a central venous line and into citrate-phosphate-dextrose bags for transfusion following cardiopulmonary bypass. The heart-lung machine was filled with Ringer's lactate solution. The proximal anastomoses were carried out before cardiopulmonary bypass by excluding a portion of the ascending aorta into which the grafts are sutured. After the proximal anastomoses were completed, cardiopulmonary bypass was instituted, the aorta was cross-clamped and the distal anastomoses were done without the use of hypothermia or cardioplegic agents. The left ventricle was not vented so that blood from the bronchial circulation and some of the blood from the right side of the heart perfused the myocardium by way of the coronary ostia and the completed grafts.

A left atrial pressure line was inserted before the cardiopulmonary bypass was discontinued and was used to monitor atrial pressures for 18 to 48 hours after operation; radial arterial pressures were also monitored during this time. Sodium nitroprusside and isoproterenol hydrochloride were used postoperatively to decrease afterload and for cardiotonic effect when indicated. The intra-aortic balloon-assist device was used postoperatively if a patient could not maintain an adequate pressure following cardiopulmonary bypass. In all, 21 patients had one graft inserted, 107 had two grafts, 82 had three grafts and 22 had four or more grafts. Of the 232 patients, 13 had anastomosis of the internal mammary artery to the left anterior descending coronary artery in addition to the vein grafts to the other arteries and 19 had right coronary endarterectomy before grafting. It was felt that optimal myocardial revascularization was accomplished.

Results

In Tables 1 and 2 are shown the preoperative pulmonary artery systolic (Table 1) and diastolic (Table 2) pressures as related to in-hospital and late deaths. Table 3 shows the preoperative left ventricular end-diastolic pressure as related to survival and Table 4 the ejection fraction as related to in-hospital and late deaths.

The five patients with the highest preoperative pulmonary artery diastolic pressures of 44 to 45 mm of mercury had left ventricular end-diastolic pressures of 22 to 40 mm of mercury and none of the five were long-term survivors. Of the 11 patients with the highest left ventricular end-diastolic pressures of 41 to 53 mm of mercury, the pulmonary artery diastolic pressure was measured in only four patients and varied from 26 to 40 mm of mercury. Six of these 11 patients were long-term survivors.

From January 1974 through December 31, 1981, the intra-aortic balloon-assist device was required in 24 of 130 patients (18%) from 1 to 76 hours (mean 38 hours). In all, 19 (79%) of these patients were discharged home. Of the last 20 patients, the intra-

TABLE 1.—*Preoperative Pulmonary Artery Systolic Pressures in 104 Patients Undergoing Myocardial Revascularization, 1969 Through December 31, 1981*

Preoperative Pulmonary Artery Systolic Pressure mm of mercury	*No. of Patients*	*In-hospital Deaths*	*Late Deaths*	*Living*
11 to 20	3	0	1	2
21 to 30	22	2	7	13
31 to 40	23	2	11	10
41 to 50	19	3	7	9
51 to 60	10	2	7	1
61 to 70	20	4	11	5
71 to 80	7	1	2	4
TOTALS	104	14	46	44

TABLE 2.—*Preoperative Pulmonary Artery Diastolic Pressure in 104 Patients Undergoing Myocardial Revascularization, 1969 Through December 31, 1981*

Preoperative Pulmonary Artery Diastolic Pressure mm of mercury	*No. of Patients*	*In-hospital Deaths*	*Late Deaths*	*Living*
0 to 10	20	1	5	14
11 to 20	35	5	15	15
21 to 30	31	3	19	9
31 to 40	13	2	5	6
41 to 45	5	3	2	0
TOTALS	104	14	46	44

aortic balloon-assist device was required in only one patient. The intra-aortic balloon-pump-assist apparatus was never used preoperatively in these patients. It is felt that with proper operative technique and anesthesia, preoperative use of the intra-aortic balloon-pump-assist device is not required to operate successfully on patients who have a poorly functioning myocardium.

A total of 58 patients were restudied from 3 months to 72 months following operation, with a mean of 31 months. The mean preoperative ejection fraction rose from 0.17 to 0.25 postoperatively ($P<.0001$). Of the 112 grafts inserted in these 58 patients, 99 (88%) were patent at the time of restudy.

Table 5 shows the preoperative and postoperative New York Heart Association functional classification of the 88 living patients. There were 13 cardiac-unrelated deaths in these patients.

Figure 1 shows the survivability of patients 50 years or younger compared with that of patients older than 50 years of age. The survivability of patients operated on who have not been in overt congestive heart failure compared with a second group in failure refractory to treatment and a third group comprising patients successfully treated for failure before myocardial revascularization is noted in Figure 2. The operative mortality was lower and the chance of long-term survival was best in those patients who had not been in clinical failure before operation. The results were poorest in those patients in failure at the time of operation. Figure 3 shows the survivability of all 232 patients operated on from August 1969 through December 31, 1981, compared with the survivability of the last 93 patients operated on from January 1976 through December 31, 1981. These two surgical groups are compared with 59 medical patients who are considered operable but who were not operated on.

During the same period from 1969 through December 31, 1981, 528 patients were operated on who had an ejection fraction of 0.21 to 0.30. The comparison of survivability in these patients can be seen in Figure 4.*

Survival curves were generated using the product-

*Jeffrey B. Garfinkle, MS, compiled the statistical data for this paper.

TABLE 3.—*Preoperative Left Ventricular End-Diastolic Pressure (LVEDP) in 169 Patients Undergoing Myocardial Revascularization*

LVEDP mm of mercury*	*No. of Patients*	*In-hospital Deaths*	*Late Deaths*	*Living†*
0 to 10	6	1	1	4
11 to 20	50	9	24	17
21 to 30	58	6	29	23
31 to 40	44	9	22	13
41 to 50	10	1	4	5
51 to 53	1	..	..	1
TOTALS	169	26	80	63

*Mean 26.
†As of December 31, 1981.

TABLE 4.—*Ejection Fractions in 232 Patients Undergoing Myocardial Revascularization, 1969 Through December 31, 1981*

Ejection Fraction	*No. of Patients*	*In-hospital Deaths*	*Late Deaths*	*Living*
0.05	4	3	1	0
0.10-0.15	96	14	53	29
0.17-0.20	132	18	55	59
TOTALS	232	35	109	88

TABLE 5.—*Preoperative and Postoperative New York Heart Association Functional Classification of 88 Living Patients*

	Class	*To IV*	*To III*	*To II*	*To I*
From	IV	2	1	18	4
	III	..	5	40	18
	II	..	..	..	..
	I	..	..	..	..

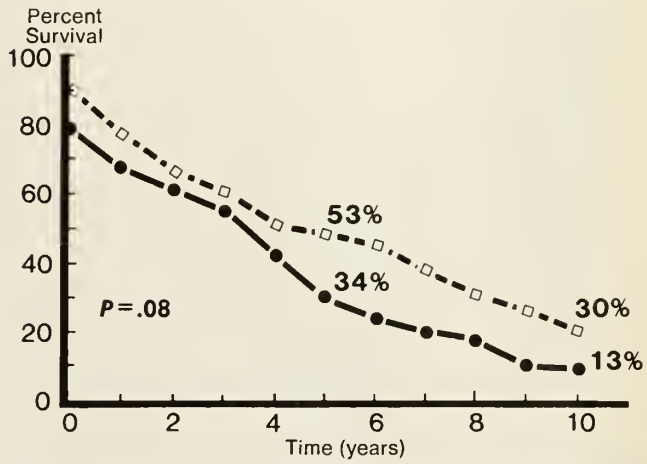

Figure 1.—Survivability of patients 50 years of age or younger (□; 61 patients) compared with those patients older than 50 years (●; 171 patients).

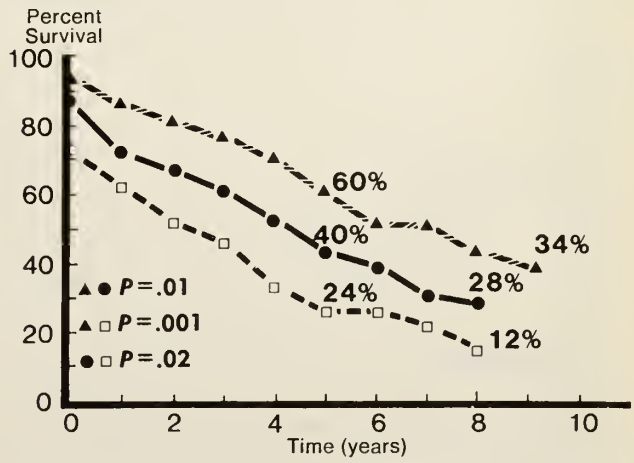

Figure 2.—Survivability comparing patients in congestive heart failure (□; 68 patients) with those with compensated failure (●; 89 patients) and patients having never been in failure (▲; 71 patients). The left ventricular end-diastolic pressures are ▲=9 to 24 mm of mercury, ●=18 to 26 mm of mercury, □=22 to 52 mm of mercury.

limit estimate described by Kaplan and Meier.[3] To test the equality of two survival curves, the statistic proposed by Breslow[4] was used. The follow-up was 100%. Three patients were lost to follow-up 5.2, 4.3 and 0.9 years after operation. Patient follow-up was accomplished by means of a questionnaire sent to physicians caring for the patients, as well as a telephone call made to the surviving patients.

Discussion

Since the publication of our article in 1977[2] that also dealt with patients who had an ejection fraction of 0.2 or less, another 92 patients have been operated on. The entire series of patients dates from August 1969 through December 31, 1981. The operative mortality was high from 1969 through 1972, with 25 in-hospital deaths in 82 patients (30%). There appeared to be no relationship between the preoperative pulmonary artery systolic or diastolic pressure and survival nor the left ventricular end-diastolic pressure and survival. In 1973, however, we started using the intra-aortic balloon pump and in 1974 nitroprusside and nitroglycerin were used in the operating room and in the intensive care unit. The mortality then decreased in the years 1973 through 1975, with 5 hospital deaths in 57 patients (9%). There was a further decrease in hospital mortality from the years 1976 through 1981, with 5 hospital deaths in 93 patients (5%). The fall in hospital mortality appears to be due to the use of nitroglycerin given intravenously in the operating room before cardiopulmonary bypass for lessening myocardial ischemia and decreasing afterload and preload, the use of nitroprusside in the postoperative period and the use of isoproterenol for its cardiotonic effect and for treating bradycardia. Atropine was also useful for treating bradycardia during operation.

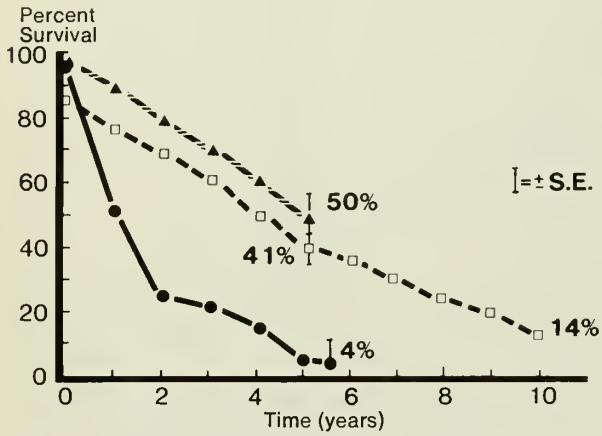

Figure 3.—Survivability for total group of 232 patients operated on from August 1969 through December 31, 1981 (□), compared with 93 patients operated on from January 1976 through December 1981 (▲) and a group of 59 medically treated patients who declined operation from March 1970 through December 31, 1981 (●). S.E. = standard error.

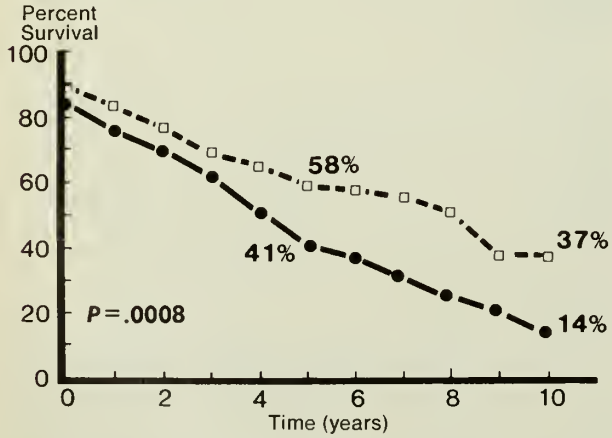

Figure 4.—Survivability of 528 patients with an ejection fraction of 0.21 to 0.30 operated on from 1969 through December 31, 1981 (□), compared with the 232 patients with an ejection fraction 0.2 or less operated on during the same period of time (●).

Improvement in operative technique has probably helped lower the in-hospital mortality, but has been thought to be of less importance than the use of the medications mentioned. The aortic anastomoses are done before bypass. The left atrium and left ventricle are not vented whereas the aorta is cross-clamped to allow bronchial blood to perfuse the completed grafts during cardiopulmonary bypass. Moderate or profound hypothermia was not used for these patients. Measuring left atrial pressure postoperatively and the judicious use of nitroprusside, chlorpromazine and isoproterenol after bypass and in the early postoperative period have been helpful in decreasing the mortality.

Analyzing data such as pulmonary artery systolic and diastolic pressures and left ventricular end-diastolic pressure has failed to show a correlation of increased pulmonary artery pressure or end-diastolic pressure and increased operative mortality or lessened long-term survival. In fact, 6 of 11 patients with a left ventricular end-diastolic pressure between 41 and 53 mm of mercury are long-term survivors with only one in-hospital death in these patients. Of five patients with a high pulmonary artery diastolic pressure of 41 to 50 mm of mercury, there were three in-hospital deaths and two late deaths.

The patients in this series were not selected for operation for angina. They may have had angina at some time in their life, but patients were not denied operation because they did not have angina in the months or years before operation.

DeRouen, Hammermeister and Dodge[5] reported that patients younger than 48 years of age or with an ejection fraction of less than 0.3 did not have a beneficial effect with operation on survival or symptoms when compared with those treated medically. Our findings with this series of patients with an ejection fraction of 0.2 or less are contrary to this. Those patients 50 years of age or younger appeared to have a better chance to survive operation and for long-term survivability than those older than 50 years. More important, however, was that patients operated on did better than those not

operated on as far as diminished symptoms and increased longevity are concerned, no matter what their age.

There was a significant difference in survivability in the 59 patients who had an ejection fraction of 0.2 or less treated medically, compared with those operated on. The medically treated patients had a survivability of 4% at five years, compared with 41% survivability at five years for the 232 patients treated surgically.

There was a highly significant difference in operative mortality and long-term results in patients who had not been in overt failure compared with those successfully treated for failure before myocardial revascularization and those who came to operation in failure. The overall in-hospital mortality for those in failure at the time of operation was 19 of 68 patients (28%); in-hospital mortality for those successfully treated for failure was 11 of 89 (12%). The operative mortality for those who had not been in overt failure at any time was 5 deaths in 72 (7%) patients operated on. At eight years the survivability was 12% for those in failure at the time of operation, 28% for those with compensated congestive heart failure at the time of operation and 34% survivability at nine years for those operated on who had not been in overt failure.

It seemed of interest to compare this group of 232 surgically treated patients with those undergoing cardiac transplantation for coronary artery disease at Stanford (California) University Medical Center. The survival of the patients with coronary artery disease at Stanford who underwent cardiac transplantation from 1971 to 1978 reported by Hassell and co-workers[6] for one year after the transplantation was 55%; for two years, 48%, and for three years, 37%. These 59 patients were between 27 and 55 years of age. Our 232 patients varied in age from 27 to 76 years, with a one-year survival rate of 72%, a two-year survival rate of 67% and a three-year survival rate of 62%.

In 1982 Pennock and associates,[7] reporting on the experiences at Stanford, listed the following primary selection criteria for cardiac transplantation: "Age 50 years or younger, normal function or reversible dysfunction of liver and kidneys." As contraindications, listed among others were

> Diabetes mellitus necessitating insulin, pulmonary vascular resistance greater than 8 Wood units and unresponsive to vasodilator drugs, symptomatic or documented severe peripheral or cerebrovascular disease, absence of adequate external psychosocial support.

Of our 232 patients, 171 (74%) were older than 50 years of age and, including the other contraindications for cardiac transplantation, few of our patients would be considered candidates for cardiac transplantation. It would appear that myocardial revascularization rather than cardiac transplantation would be indicated for most patients who have an ejection fraction of 0.2 or less. The results with revascularization seem better than with transplantation for this group of patients.

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Epidural Administration of Morphine Postoperatively for Morbidly Obese Patients

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Two groups of morbidly obese patients undergoing a gastric stapling procedure were compared. Patients in group I received 5 mg of morphine through a lumbar epidural catheter immediately after the surgical procedure while group II patients were treated conventionally with parenterally administered morphine. In group I less narcotics were needed and patients were able to walk earlier than in group II. Length of hospital stay, time to removal of the nasogastric tube and postoperative pulmonary function were not significantly different between groups. Two patients in group I and one patient in group II had generalized pruritus, and in one study patient bradypnea developed in association with the epidural administration of morphine. It is concluded that morbidly obese patients can benefit from epidurally administered morphine and that this form of therapy has a role in the management of these patients.

(Brodsky JB, Merrell RC: Epidural administration of morphine postoperatively for morbidly obese patients. West J Med 1984 May; 140:750-753)

The surgical care of morbidly obese patients represents a formidable challenge to surgeons, anesthesiologists and nursing personnel. The logistics of this care call for careful planning to avoid the otherwise high incidence of postoperative complications. These patients frequently have coexisting pulmonary, cardiovascular and metabolic problems and can decompensate very quickly with little physiologic reserve to assist recovery.[1] The overriding principle in their care is avoidance of complications because the treatment of established complications, either pulmonary or strictly surgical, is extremely difficult.

In developing a regimen that minimizes the likelihood of pulmonary problems in particular, postoperative narcotic use should be minimal, but at the same time patient cooperation and, therefore, comfort are absolutely essential. In an effort to develop a regimen that would at once reduce narcotic requirements and enhance patient mobility and subjective comfort, we examined the effect of administering epidurally morphine at the end of operation through a catheter placed preoperatively.

Patients and Methods

This study was approved by the Human Subjects Committee of Stanford University School of Medicine. Informed written consent was obtained from 12 morbidly obese female patients undergoing an elective abdominal gastric stapling operation. Morbid obesity was defined as a doubling of ideal weight as determined from the standard Metropolitan Life Insurance Company height-weight table.

Patients were randomly separated into two study groups. Group I patients had a catheter placed in a lumbar epidural space. They were then given 1.5% lidocaine hydrochloride solution, 20 ml, before the surgical procedure to assess the proper position of the catheter. After a definite level of anesthesia was noted, induction of general anesthesia proceeded. Group II (control) patients were given no epidural drugs. Both groups received thiopental sodium intravenously, 350 to 650 mg, followed by intravenous administration of succinylcholine chloride, 100 to 120 mg, to facilitate endotracheal intubation. All patients were ventilated with a controlled-volume ventilator and received either

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enflurane or isoflurane during the operation. Additional lidocaine or bupivacaine hydrochloride was used as needed to supplement the general anesthetic in group I patients, but no patient in this group received narcotics during the operation. Patients in group II were given meperidine hydrochloride intravenously or fentanyl citrate intraoperatively. Pancuronium bromide was used in both groups when necessary to provide muscle relaxation.

All patients were awake and had their trachea extubated within 15 minutes following the completion of the operation. Group I patients were given 5 mg of preservative-free morphine (A. H. Robins Company, Richmond, Virginia) in 10 ml of saline via the epidural catheter on arrival in the surgical intensive care unit. If after 30 minutes any patient complained of incisional pain, morphine was given intravenously in small increments to alleviate the pain. For the remainder of the hospital stay, patients in both groups received narcotics parenterally whenever there was a need for analgesia.

TABLE 1.—*Parenteral Doses of Morphine and Side Effects*

	Mean Dose (Range)	
Postoperative Days	*Group I (Epidural) mg N=6*	*Group II (Control) mg N=6*
1	1.8 (0 to 5)	19.8 (8 to 35)
2	5.8 (0 to 15)	40.6 (20 to 100)
TOTAL	39.0 (0 to 90)	119.0 (56 to 232)
Side Effects		
Pruritus	2 patients	1 patient
Bradypnea	1 patient	no patient
Urinary retention	?	?
Central nervous system depression	no patient	no patient

The interval from the time the morphine was given epidurally until parenteral narcotics were necessary was noted in group I patients. The total amounts of narcotic administered were recorded for all patients. Arterial blood gas determinations and spirometric pulmonary function studies were done in all study patients on the mornings of the first and second postoperative days. The time to ambulation, the time to removal of the nasogastric tube and any postoperative complications were recorded.

Results

Patients in groups I and II were similar in age and weight (33.8±6.8 years versus 34.0±10.0 years, 135.8 ±13.4 kg versus 123.8±15.9 kg; mean ± standard deviation [SD]). On the first two postoperative days group II patients required about eight times more morphine parenterally than did group I patients (Table 1). Two patients in group I did not need any additional narcotics on these two days, and one of these patients did not require further narcotics at all during her six days in the hospital postoperatively. Pain relief from the morphine given epidurally lasted from 20 hours to 6 days, with minimal supplementation with parenteral morphine required during the first two postoperative days. Two patients in group I and one patient in group II complained of pruritus, and one patient in group I had a significant slowing of her respiratory rate after receiving morphine epidurally (Table 1). Five of the six patients in group I were out of bed and ambulating within 24 hours compared with two of six patients in group II. The length of hospital stay and the interval between the completion of operation and the removal of the nasogastric tube were similar for all patients (Table 2). There were no significant differences in

TABLE 2.—*A Comparison of Patients Receiving Morphine Epidurally With Patients Receiving Morphine Parenterally*

	Group I (Epidural) N=6	*Range*	*Group II (Control) N=6*	*Range*
Mean time to ambulate (hours)	15.5	5 to 27	26.5	5 to 46
Mean time to removal of nasogastric tube (hours)	70.3	46 to 96	76.3	68 to 98
Mean postoperative hospital stay (days)	5.5	4 to 7	6.3	5 to 8

TABLE 3.—*Postoperative Pulmonary Function*

Postoperative Days	*Group I (Epidural) N=6*	*Range*	*Group II (Control) N=6*	*Range*
Day 1				
Mean Po_2* (mm of mercury)	67.7	55 to 83	64.7	55 to 85
Mean Pco_2* (mm of mercury)	36.2	33 to 40	40.2	34 to 48
Mean vital capacity (liters/min)	1.8	1.0 to 2.9	1.5	0.9 to 2.1
Day 2				
Mean Po_2* (mm of mercury)	70.1	59 to 81	64.0	51 to 80
Mean Pco_2* (mm of mercury)	37.5	35 to 43	38.4	33 to 44
Mean vital capacity (liters/min)	2.0	1.0 to 2.5	2.1	1.1 to 3.6

Po_2=oxygen partial pressure, Pco_2=carbon dioxide partial pressure.

*Determination made with the patients breathing room air.

pulmonary function between the two groups on the first two postoperative days (Table 3).

Discussion

Local anesthetics administered epidurally for analgesia must be given in small doses to avoid sympathetic blockade with resultant hypotension. Concomitant with the analgesia, motor function may be impaired, preventing coughing to clear secretions, movement and ambulation. In addition, frequent supplementation of the local anesthetic is necessary to provide continuous pain relief. These potential problems are magnified in the care of an obese surgical patient. Preexisting circulatory and respiratory problems mandate that local anesthetics be carefully titrated to avoid undesirable side effects. The increased incidence of venous thrombosis and subsequent pulmonary embolism in obese patients necessitates that these patients ambulate as soon as possible after an operation,[1] and the motor blockade from local anesthetics given epidurally can prevent this.

Epidural administration of morphine seems ideal for morbidly obese patients. Opiate narcotics administered in the epidural space work at the spinal level and are quite effective in treating incisional pain without the usual narcotic depression of the higher centers of the central nervous system.[2-5] Pain relief is excellent and long lasting. The analgesia from epidurally given narcotics is selective because only the subjective experience of pain is blocked. In our study, the analgesia was satisfactory in all patients who received morphine epidurally but was not always absolute. Very small amounts of parenteral narcotics were necessary to supplement the epidural morphine on the first and second postoperative days in four of the six group I patients. Many factors influence individual response to this form of therapy. For example, the analgesia from epidurally administered morphine is greater if the narcotic is given before the onset of pain.[2] Patient expectations and psychologic background are important in assessing the success of epidural administration of morphine. Not all discomfort following an abdominal operation is from the wound itself.[6] Because morphine given epidurally is effective in treating incisional pain, patients often focus their attention on other unpleasant sensations such as the discomfort from the nasogastric tube. The patients in group I appeared much more comfortable during the first two postoperative days than group II patients to us and to the nurses caring for them. However, formal analgesic scoring was not done. Numerous previous studies have shown the superiority of epidural over parenteral administration of morphine in providing postsurgical analgesia.[2-5]

Five of the six patients who received morphine epidurally were out of bed and walking within 24 hours after the operation compared with two of the six patients in the conventionally treated group. This, plus the reduced narcotic requirements, seems to be the main advantage of this treatment because pain relief and earlier ambulation are likely to be reflected in reduced incidence of postoperative pulmonary and thromboembolic complications. Because of the small size of our study groups, however, significant differences in the rate of these complications could not be documented.

Obesity can be associated with serious respiratory abnormalities, particularly following abdominal operations.[7] There were no differences between study groups in arterial blood gas levels or forced vital capacity on the first and second postoperative days. No differences in postoperative pulmonary function have also been reported in nonobese patients receiving morphine epidurally after upper abdominal operations.[8] Although clinically significant respiratory depression has been associated with epidural morphine, this complication is rare.[2,9] In only one patient in 1,200 who received morphine epidurally did significant respiratory symptoms develop postoperatively in one large series.[9] One of our group I patients had a slowing of her respiratory rate from 16 breaths per minute to 10 breaths per minute 20 minutes after receiving morphine epidurally. This was immediately reversed with administration of naloxone hydrochloride without affecting analgesia. The respiratory problems associated with epidurally given narcotics occur within 24 hours (usually within two to four hours) of administration.[3] We therefore recommend that nursing personnel closely observe and monitor for at least 24 hours patients receiving morphine epidurally. The potential for respiratory problems with parenteral administration of narcotics may actually be greater than that associated with narcotics given epidurally.[9]

Epidural administration of anesthesia has definite advantages in the intraoperative management of morbidly obese patients.[10] Using local anesthetics for analgesia and for motor blockade during operation allowed us to use less general anesthesia and muscle relaxant in group I patients. Two group I patients did not require any pancuronium and therefore there were no potential problems with reversal of muscle relaxants at the end of the procedure in these patients.

Urinary retention occurs in as many as 20% of patients receiving morphine epidurally.[4,9] All of our patients had an indwelling urinary catheter so the incidence of this complication could not be assessed. Renal responses in patients receiving narcotics epidurally do not differ from those of patients receiving parenteral narcotics.[5] Two patients in group I had mild generalized pruritus after receiving preservative-free morphine. It has been suggested that pruritus is a side effect of preservatives,[4] but this complication has also been noted previously in patients who received preservative-free morphine.[11] Interestingly, one patient in group II also complained of pruritus.

Central nervous system depression following the epidural administration of narcotics is less than that following similar dosages of intravenously given narcotics,[12] and no patient in our study had this problem. Nausea and vomiting are also less frequent with epidu-

ral administration of morphine than after morphine given parenterally.[4] The nature of the surgical procedure in our study made determination of this complication difficult. The time of removal of the nasogastric tube was used as a crude measure of bowel function. Both groups I and II patients had their nasogastric tubes removed on the third postoperative day.

In conclusion, we found that pain relief from epidural administration of morphine in morbidly obese patients was highly satisfactory and that these patients required significantly less narcotics than similar patients given narcotics parenterally. There were no differences in respiratory function postoperatively between study groups. Patients who received morphine epidurally were out of bed and ambulating earlier than conventionally treated patients. We believe that epidural administration of morphine is a useful adjunct in the postoperative care of morbidly obese surgical patients.

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Medical Progress

Hepatitis B Virus Infection

Current Concepts of Chronicity and Immunity

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Among the three types of viral hepatitis agents—A, B and non-A, non-B—the hepatitis B virus (HBV) has been best characterized by immunologic and recombinant DNA technologies. The indefinite persistence of hepatitis B virus infection in 85% to 90% of perinatally infected infants and in about 10% of those infected later in life accounts for a worldwide epidemiologic reservoir of more than 200 million carriers who are at a high risk for the development of δ-infection, chronic liver disease and hepatocellular carcinoma. Active immunization with a safe and effective vaccine, derived from the plasma of carriers of hepatitis B surface antigen (HBsAg), is envisaged to avoid viral hepatitis type B and its chronic sequelae. In addition to serologic and immunohistochemical markers of hepatitis B virus infection, hybridization assays using cloned HBV DNA have provided new insight into the biology of this virus, its persistence and its oncogenic potential in humans and in animal models. Genetic similarities have been recognized between HBV and the antigenically distinct non-A, non-B agents implicated in some cases of transfusion-associated chronic hepatitis. Structurally this unique group of HBV and HBV-like agents are DNA viruses with functional attributes of integration and replication analogous to the retroviruses.

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An elevated serum alanine aminotransferase (ALT) level indicates hepatocellular damage caused by a variety of drugs, alcohol, toxins, inherited metabolic disorders and hepatotropic viral agents such as hepatitis A virus (HAV), hepatitis B virus (HBV) and the non-A, non-B viruses. Persistence of abnormal serum ALT levels for more than six months is suggestive of chronic liver disease, most frequently associated with serologic evidence of viral hepatitis. Immunodiagnosis has been useful in distinguishing the etiology and outcome of unresolved viral hepatitis, and liver biopsy is used to establish the histologic diagnosis of chronic liver disease.

Sensitive and specific serologic tests for hepatitis A and B virus infections permit differentiation of clinically indistinguishable episodes of viral hepatitis.[1] Whereas IgM anti-HAV is diagnostic of acute hepatitis A, IgG anti-HAV is indicative of past infection and lifelong immunity. Because no chronic sequelae follow infection with hepatitis A virus, it is not implicated in chronic liver disease. In contrast, acute hepatitis B virus infection remains unresolved in about 10% of adults and 90% of newborns and is definitely implicated in the development of chronic liver disease. Antigenic markers of HBV include the hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg) and the "e" antigen (HBeAg), and immune response to them leads to the detection of anti-HBs, anti-HBc and anti-HBe, respectively, in the serum of an infected host. The invariable occurrence of HBsAg and anti-HBc, and a specific lack of immune response to HBsAg, characterize the HBV carrier state in an estimated 750,000 Americans and 200 million people in the world who are at a very high risk for the development of chronic liver disease and hepatocellular carcinoma.[2]

After excluding various causes by carefully eliciting

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
anti-HAV = antibody to hepatitis A virus
anti-HBc = antibody to hepatitis B core antigen
anti-HBe = antibody to hepatitis B e antigen
anti-HBs = antibody to hepatitis B surface antigen
HAV = hepatitis A virus
HBcAg = hepatitis B core antigen
HBeAg = hepatitis B e antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus

the clinical history and doing appropriate serologic tests for hepatitis A and B virus infections, negative findings lead to a deductive diagnosis of non-A, non-B hepatitis, so called for lack of a better term for this heterogeneous entity. The non-A, non-B forms of hepatitis may be caused by more than two agents, which are transmissible in chimpanzees, without any cross-protection.[3,4] Therefore, a serologic test for the detection of several agents involved in non-A, non-B hepatitis has not been possible to date. Using ALT elevation in the absence of serologic markers of hepatitis A and B viral infections, the non-A, non-B hepatitis has been recognized as a major complication of blood transfusion in 8% to 10% of transfused patients, with chronic liver disease developing in about 40% of such patients.[5,6]

Among the agents of three types of viral hepatitis summarized in Table 1, the most extensive information has been gained about HBV.[7] Our current understanding of the biology of HBV,[8] the natural course of infection and its epidemiology[9] and, finally, the means of active and passive prophylaxis[10] originated from the discovery of the Australia antigen (HBsAg) in 1965.[11] Preventing perinatal viral hepatitis type B is bound to ultimately reduce the prevalence of the chronic carrier state and consequent chronic liver disease and hepatocellular carcinoma.[12-15] The safe and effective but expensive vaccine currently made from the plasma of HBsAg carriers may be superseded by new vaccines produced by recombinant DNA technology or by peptide synthesis, if they prove to be more economical, especially for perinatal use in highly endemic Asian and African nations. Although the pathogenetic mechanisms underlying hepatocellular injury in acute and chronic liver disease are not defined and are largely hypothetic, the cloned HBV DNA permits hybridization assays that are used in understanding the persistence of infection underlying chronic liver disease and hepatocellular carcinoma.

HBV and HBV-like Hepadna Agents

The high level of the nucleic acid-free envelope protein occurring as 22-nm particles in the plasma of infected persons permits serologic detection of HBsAg. The infectivity of HBV in serum experimentally inoculated into chimpanzees and humans is 1,000 to 10,000 times higher than the detection limits of HBsAg in the most sensitive radioimmunoassays.[7,16] Furthermore, an HBsAg-positive, HBeAg-positive specimen is more than 30,000 times more infectious than an HBsAg-positive, HBeAg-negative serum. Thus, serum HBeAg is an indicator of high infectivity. In fact, serum and blood products can be infectious despite negative findings for HBsAg by radioimmunoassay used in screening blood, as evidenced by the 5% to 10% incidence of viral hepatitis type B in cases of posttransfusion hepatitis.[6]

The hepatitis B virion (Dane particle) contains HBcAg, HBeAg, a partially double-stranded DNA of about 3.2 kilobases, DNA polymerase and a protein kinase activity within the core that is fully enveloped by HBsAg (Figure 1). Because of the DNA homology, polypeptide similarities and antigenic cross-reactivity between HBV and other distinct hepatotropic viruses found in woodchucks, ground squirrels and ducks,

TABLE 1.—*Characteristics of Three Types of Viral Hepatitis*

	Type A	*Type B*	*Type Non-A, Non-B*
Nucleic acid	RNA (single stranded)	DNA (double stranded)	Unknown
Class	Enterovirus	Hepadna	Unknown
Incubation period (days)	15 to 45	45 to 150	20 to 70
Mode(s) of transmission	Fecal-oral	Percutaneous Oral-oral Venereal Perinatal	Percutaneous Perinatal Fecal-oral
Transfusion-related hepatitis (%)	0	5 to 10	90 to 95
Sporadic hepatitis (%)	20 to 30	50 to 60	~20
Progresses to chronic hepatitis	No	Yes (≃10%)	Yes (10% to 40%)
Asymptomatic carrier state	No	Yes	Yes
Chronic liver disease	No	50%	50%
Associated with hepatocellular carcinoma	No	Yes	Unknown
Preexposure prophylaxis			
Active	None available	Vaccine	None available
Passive	ISG	HBIG	ISG

ISG = immune serum globulin; HBIG = hepatitis B immune globulin

these agents are called Hepadna (hepatotropic DNA) viruses.[17] The occurrence of chronic liver disease and hepatocellular carcinoma in persistently infected woodchucks has provided an animal model for the study of pathogenetic mechanisms at the molecular level.[18] Similarly, the duck hepatitis B virus has provided an insight into the novel replication of the viral genome by reverse transcription of an RNA intermediate.[19] Analysis of viral DNA molecules in liver and serum of infected chimpanzees suggests that most of the Dane particles represent defective noninfectious virus and that particles with supercoiled DNA may indeed represent the infectious virion.[20] Entry of HBV in human hepatocytes is apparently mediated by a receptor specific for the HBV-envelope protein.[21] Despite the failures to grow normal human hepatocytes in culture and to propagate HBV in vitro, we have indirectly acquired a remarkable understanding of the hepatocellular replication of HBV. During entry into the hepatocytes, the HBV DNA must be uncoated and processed through a series of replicative steps illustrated in Figure 2.

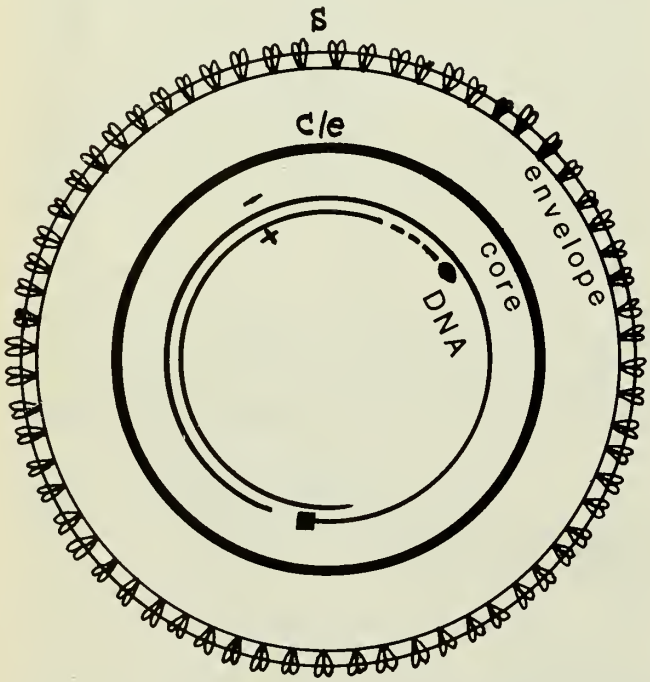

Figure 1.—Diagramatic representation of hepatitis B virus with the envelope carrying the hepatitis B surface antigen and the core carrying the hepatitis B core antigen (HBcAg), indicated as S and C, respectively. The envelope consists of a lipid bilayer embedding 50 to 60 dimeric subunits of the virally encoded 25,000 daltons protein and its glycoprotein derivative of 29,000 daltons. Upon removal of the envelope with nonionic detergents, the HBcAg becomes detectable. When the cores are denatured by sodium dodecyl sulfate, the HBcAg activity is lost and hepatitis B e antigen activity is detected in the core peptides. The circular double-stranded DNA is contained within the hepatitis B virus core. The minus strand has a nick and a protein attached to its 5′ end. The plus strand of variable length is elongated by the action of the endogenous polymerase to form a fully double-stranded molecule of hepatitis B virus.

Whereas HBV is transmissible only to humans and chimpanzees, the genetic analyses of cloned DNA of various Hepadna viruses have shown a remarkable degree of phylogenetic relationship.[8,17] For example, the complete nucleotide sequence of HBV and woodchuck hepatitis virus showed striking similarities, with the highest degree of homology in the gene encoding the core protein.[22] It is also remarkable that Trepo and co-workers have found cross-reactivity between the core proteins of HBV and the so-called non-A, non-B agents associated with chronic liver disease.[23] Accumulating epidemiologic evidence indicates that viruses genetically related to HBV, but antigenically distinct, may be responsible for some cases of chronic liver disease, including cases of posttransfusion hepatitis.[24-26] Because Wands and associates[27] have experimentally shown, by inoculating chimpanzees, that some of the non-A, non-B agents are in fact HBV-like, the Hepadna group of agents may expand. It must, however, be emphasized that several of the infectious non-A, non-B agents in factor VIII concentrates and other documented inocula are unrelated to HBV.[28] Other than infectivity established by transmission from humans to humans, from humans to chimpanzees and from chimpanzees to chimpanzees, these non-A, non-B agents are largely uncharacterized.

The restriction endonuclease analyses of cloned HBV DNA have shown genetic similarities between several of the Hepadna viruses.[8,17,22,29] A single Eco RI site, common in various Hepadna viruses,[8,15,17] is used as a reference point in the genetic map of HBV shown in Figure 3. Complete nucleotide sequencing of cloned DNA of hepatitis B and woodchuck hepatitis viruses has been done by several investigators.[22,30-32] The genes C and S encoding the core and the envelope proteins

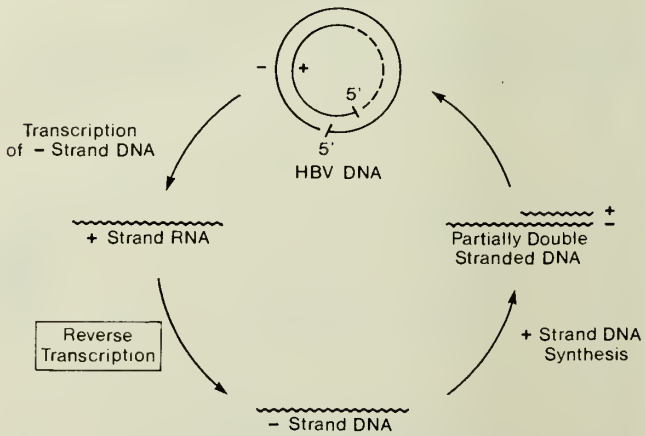

Figure 2.—A simplified model of hepatitis B virus (HBV) replication analogous to duck HBV.[19] The Hepadna agents comprise unique DNA viruses with functional characteristics of a retrovirus—that is, replication of viral DNA through an RNA intermediate and reverse transcriptase. The minus strand of the HBV is used as a template in the transcription generating a plus-strand RNA, which in turn is reverse transcribed to a minus-strand DNA. Synthesis of plus-strand DNA leads to partially double-stranded DNA.

of HBV respectively have been localized and the segment encoding the major antigenic determinants a and d/y has been localized in the middle of gene S.[15] The polymerase gene and an undefined gene X, potentially capable of coding for a protein, are hypothetic propositions. A remarkable similarity in the molecular biology of phylogenically separate HBV and duck HBV is illustrated by the occurrence of asymmetric replicative intermediate forms of HBV DNA in human liver (Blum and colleagues, unpublished observation, September 1983), as well as the detection of the viral DNA and the gene products in cells other than hepatocytes.[15,33]

Chronic Viral Hepatitis Type B

The natural history of hepatitis B is varied and complex.[34-36] Three forms of hepatitis B are encountered in clinical practice: acute hepatitis B, inapparent sporadic episodes of unknown origin and the chronic carrier state—detected by screening for HBsAg—in apparently healthy persons. Perinatal transmission of hepatitis B, especially from an HBeAg-positive mother to her newborn, leads to indefinite persistence of the infection in about 85% to 95% of the infants[37]; in contrast, only 10% of persons who have the primary infection later in life remain persistently infected.[36] Immune complexes containing HBsAg and IgM persisting in about 7% of patients with acute hepatitis B have been reported to be a predictor of chronicity.[38] This remarkable observation merits confirmation.

Chronic hepatitis B is typically characterized by high levels of HBsAg, HBeAg, anti-HBc, serum HBV DNA detected by dot blot hybridization, DNA polymerase and varying elevations of the serum ALT level reflecting active virus replication and liver disease activity.[39] Seroconversion from HBeAg to anti-HBe in chronic carriers is often preceded by acute exacerbation of chronic hepatitis.[39-41] Thus, carriers of HBV do not have two separate forms—that is, disease and "healthy" carrier state. Rather, there are two stages of chronic hepatitis type B[39]: an early phase of 1 to 20 years during which hepatitis disease activity may be present with HBeAg in the serum, and a later stage when necroinflammatory activity ceases and seroconversion to anti-HBe has occurred.

So-called healthy carriers are most frequently detected by screening blood donors and health care workers for HBsAg. The natural history of liver disease in asymptomatic carriers has been prospectively investigated in several studies.[42-48] Despite qualitative and quantitative differences, these studies have shown subclinical forms of liver disease from abnormalities noted on liver function tests, HBeAg and a spectrum of histologic abnormalities. More men than women, more young adults than older people and more Asians than whites have chronic carrier state without apparent liver disease. Among carriers a seroconversion from HBeAg to anti-HBe occurs progressively with age.[49]

A spontaneous clearance of HBsAg has been noted annually in about 2% of carriers.[43] Because carriers have a greater susceptibility to the hepatotoxic effect

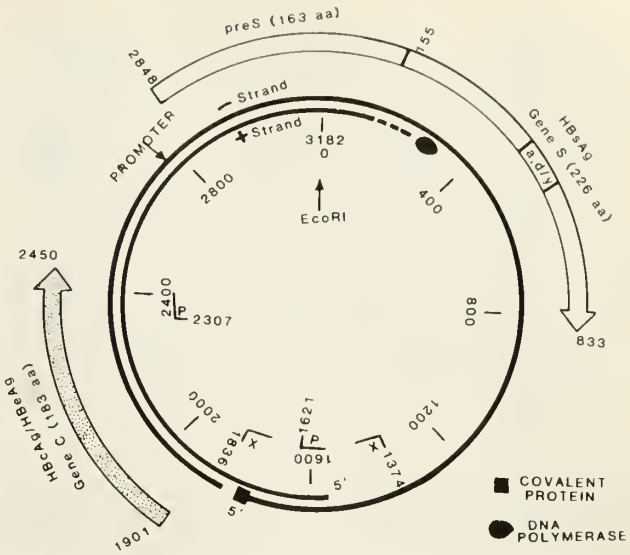

Figure 3.—Genetic organization of the HBV genome with a single Eco RI site used as a point of reference. The 5′ end of the minus strand is base-paired with the 5′ end of the plus strand with a cohesive overlap of 200 to 300 nucleotides to render a circular form. The broad arrows surrounding the genome indicate the open regions of the minus-strand transcripts that encode the two identifiable products of gene C and gene S. A hypothetical transcript of nucleotides 2307 to 1621 in the clockwise orientation could encode the endogenous polymerase (gene P), and the region between 1374 and 1836, marked X, potentially encodes an unidentified gene product. A promoter of gene S has been experimentally localized immediately preceding the pre-S region.[8] HBcAg = hepatitis B core antigen, HBeAg = hepatitis B 'e' antigen, HBsAg = hepatitis B surface antigen.

of alcohol[50] and the evidence of a high rate of hepatitis B is recorded in cases of alcoholic cirrhosis and hepatocellular carcinoma,[51,52] it may be advisable for carriers to abstain from alcohol. Chronic hepatitis B appears to be a dominant cause of chronic liver disease, classified as a variety of distinct disease states associated with characteristic histologic expression, such as degrees of portal inflammation, chronic persistent hepatitis, chronic active hepatitis with or without cirrhosis and fatty liver with large cytoplasmic fat globules. The natural course of HBsAg-positive chronic active hepatitis is progressive, frequently evolving to cirrhosis, hepatocellular carcinoma and death due to liver failure or bleeding esophageal varices.[53] The use of corticosteroids certainly has no value in treating HBV-related chronic active hepatitis; in contrast, autoimmune hepatitis may respond favorably to steroid therapy.[54]

Although the definition of viral hepatitis type B is generally established by serologic methods, the immunohistochemical diagnosis on liver tissue may permit the detection of hepatitis B in patients who are seronegative or who have anti-HBs as the marker of immunity to HBV infection.[24] Recently ^{32}P-labeled cloned HBV DNA has been used as a probe in the Southern blot analysis of hepatocellular DNA extracted from the tissue of patients with chronic liver disease.[24,26,51] Both free and integrated HBV DNA are detected in the liver of chimpanzees and humans with chronic hepatitis.[47,56,57]

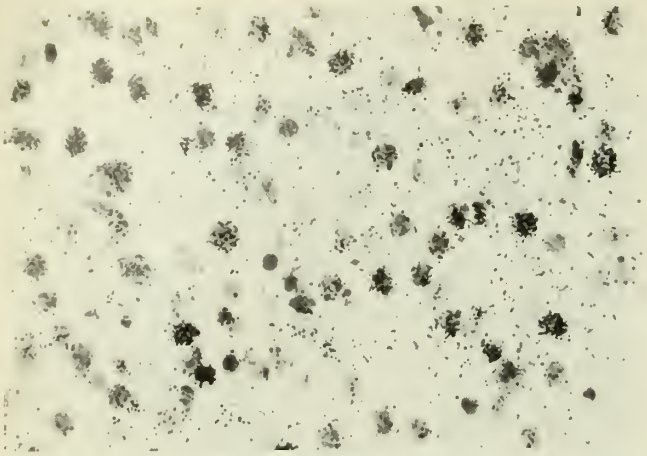

Figure 4.—In situ hybridization pattern of hepatitis B virus (HBV) DNA in the liver tissue from a patient with chronic persistent hepatitis. The HBV DNA is localized focally in the nuclei of infected cells.

Free viral forms predominate in the early stages of chronic hepatitis type B with HBeAg in the serum, and integrated forms predominate in later stages of chronic hepatitis B.[57] No specific pattern of integration is recognized as a correlate of chronicity or oncogenicity. Thus, DNA hybridization in Southern blot analysis provides direct evidence of HBV DNA in the hepatocellular tissue not only when serologic evidence for viral hepatitis is definite but also when serologic markers are absent. In fact, HBV DNA has been found in at least seven patients with chronic liver disease[24,26] and seven with hepatocellular carcinoma[51] who lacked all serologic markers of hepatitis B. Thus, patients with serologically defined non-A, non-B hepatitis may have chronic liver disease and hepatocellular carcinoma without expression of the gene products of HBV present in their hepatocytes. This biologic anomaly may be due to methylation of cytosine in HBV DNA that can profoundly influence DNA replication, control of transcription, establishment of preferred sites for mutations and oncogenic transformation.[58] Such methylation has been shown to account for selective failure to express gene C in the PLC/PRF/5 hepatoma cell line.[59] These observations raise new questions about the validity of the current serologic definition of non-A, non-B hepatitis; conceivably, HBV-like agents are involved in causing non-A, non-B chronic hepatitis. Immunohistochemical and DNA hybridization assays provide results that further confuse the serologic definition of non-A, non-B hepatitis.

Most recently the technique of in situ hybridization has been applied to understanding the pathogenesis of chronic liver disease due to hepatitis type B.[60] The major advantage of this difficult but powerful method lies in the use of only a fraction of the liver biopsy specimen obtained for diagnostic purposes. We found 1,000 to 2,000 copies of viral DNA per infected hepatocyte having a focal distribution amid several noninfected hepatocytes shown in Figure 4. This assay will also be useful in assessing the efficacy of antiviral agents such as interferon and Ara-A in the treatment of chronic liver disease.

Recently we have noted unexpected dissemination of hepatitis B virus infection in the cells of vascular endothelium, bile duct epithelium, germinal centers of the spleen, bone marrow, blood leukocytes and Kaposi's sarcoma.[60] These diverse observations raise a possibility that HBV may have a role in the acquired immune deficiency syndrome (AIDS) and in the oncogenic sequelae of nonhepatocellular infection by the virus.[60]

δ-Agent in Chronic Hepatitis B

The studies by Rizzetto and colleagues have established the clinical importance of the δ-agent that needs the hepatitis B virus as a covirus.[61,62] Carriers of HBV may have a superimposed acute δ-infection that is generally detected by serologic test for anti-δ in the serum.[61] The δ-agent is a small (0.8 kilobases) RNA agent transmissible to humans and chimpanzees with hepatitis B. δ-Antigen is generally undetectable in the serum but it is detectable in the nuclei of hepatocytes by means of fluorescent anti-δ antibodies.[62] When superimposed on a chronic carrier state, δ-infection tends to be chronic with significant persistence of IgM anti-δ in the serum.[63] The morbidity and mortality of δ-infection is remarkably high.[62,63] Although originally described in drug addicts in Italy, δ-infection occurs worldwide, as shown by detection of anti-δ in different countries.[61] Apparently patients with chronic active hepatitis and chronic δ-infection have a remarkably progressive course. In a recent epidemic of δ-infection in HBV carriers in Venezuela, an alarmingly high mortality rate has been noted.[63] Although drug addicts are a principal reservoir of δ-infection, homosexual men and other carriers of HBV are at an increased risk for the development of δ-associated chronic active hepatitis. Further data are being collected by Redeker, who finds the prevalence of δ-infection high among patients who have chronic liver disease.[63] Several of the recent reports on chronic δ-infection associated with hepatitis B have increased the awareness of its high pathogenicity and chronicity.[62]

Hepatocellular Carcinoma

Accumulated epidemiologic data compel us to consider HBV as a causative agent of hepatocellular carcinoma.[2] The effects, however, of known hepatic cocarcinogens such as hormones,[64] aflatoxin B_1,[65-67] alcohol,[51,52] cottonseed oil[68] and vinyl chloride[64] must be considered in the etiology of hepatocellular carcinoma, especially because of the remarkably low incidence of hepatocellular carcinoma in Greenland, which has one of the highest prevalences of chronic HBsAg positivity.[69]

In a prospective study of 22,707 men in Taiwan, Beasley and co-workers[70] determined that HBsAg carriers have a 223-fold higher risk of hepatocellular carcinoma developing than do noncarriers. Thus, hepatitis B clearly plays a primary role in causing hepatocellular carcinoma. Although uncommon in whites, hepatocel-

lular carcinoma is the commonest cancer in the world, with a prevalence paralleling the incidence of HBsAg. Worldwide, there are 250,000 new cases of liver cancer each year, potentially preventable by mass immunization against primary hepatitis B.[13] Based on a case of perinatally acquired hepatitis B and the detection of hepatocellular carcinoma after seven years, apparently the period from infection to evolution of carcinoma may vary between 7 and 70 years.[70,71] This is consistent with the observation of Heyward and colleagues that hepatitis type B occurred as little as ten years before the recognition of hepatocellular carcinoma in Alaskan Eskimos.[72] They noted significant elevation of α-fetoprotein levels two years preceding seroconversion from HBeAg to anti-HBe and six years preceding the clinical onset of hepatocellular carcinoma.[72]

The association between viral hepatitis type B and hepatocellular carcinoma is substantiated by the common observation of HBV DNA integrated in the host DNA of hepatocellular carcinoma tissue and hepatoma cell lines.[8,24,55,73-77] Despite integration of HBV DNA in hepatocellular DNA of tumors, the mechanisms of integration, pattern or specificity of integration and associated oncogene(s) remain largely undefined.[78] On the other hand, not all hepatocellular carcinomas in HBV-infected persons show viral DNA in the tumors, thus raising a doubt about the exclusive oncogenic role of HBV in primary hepatocellular carcinoma (W. S. Robinson, MD, presented at the International Symposium on Viral Hepatitis, San Francisco, March 1984).

Besides surgical removal of the liver cancer, the combined modality of therapeutic regimens includes irradiation, chemotherapy, hormonal therapy[79] and experimental isotopic immune globulin therapy. Reduced glutathione is a harmless natural product that has been shown to cause impressive survival with regression of aflatoxin-induced hepatocellular carcinoma in experimental animals.[80] This agent offers a new candidate in still-evolving therapeutic regimens for hepatocellular carcinoma.

Prevention of Hepatitis B by Vaccination

The protective effect of anti-HBs against hepatitis B infection has led to the use of a vaccine consisting of the 22-nm particles of viral envelope protein isolated from the plasma of HBsAg carriers.[10] A large body of data on clinical trials, safety and efficacy of the HBsAg vaccines has been published in the proceedings of different symposia.[9,15,81] In the United States a safe and effective vaccine produced by Merck Sharp & Dohme, Heptavax-B, has been licensed for clinical use; similarly, in Europe vaccines made by Institute Pasteur of France, as well as Merck Sharp & Dohme, have been licensed. Both of these vaccines use highly purified HBsAg following inactivation with formalin and alum as adjuvant. The Central Laboratory of the Netherlands Red Cross used a different process of purifying HBsAg with heat inactivation at 101°C for 90 seconds and the final product heated at 65°C for 11 hours. This vaccine is also safe and effective in the clinical trials recently reported at the World Health Organization/International Association of Biological Standardization Symposium in Athens (November 1982). Thus, the American, French and Dutch vaccines containing 20, 5 and 3 μg of HBsAg per dose, respectively, are highly immunogenic, safe and effective in providing sustained protection against a serious infection that causes acute and chronic liver disease. Although long-term follow-up is not available, most of the vaccinees have elicited anti-HBs response for as long as three years. Several of the early vaccinees have shown protection and anti-HBs for a period exceeding five years. Most important, HBsAg of one subtype used in the vaccine is protective against viral hepatitis of other serotypes.

The vaccine is given intramuscularly in three doses over a period of six months. Following the first dose, more than 50% of the vaccinees have serologic evidence of anti-HBs response. The second dose of the vaccine is given one to two months later, and a third dose is administered six months after the primary immunization. After completion of the course of three doses, more than 95% of the persons are successfully immunized. Nonresponders or hyporesponders may be given a second set of injections. At the present time there is no recommendation for the management of nonresponders. It must be emphasized that the inactivation procedures have been shown to destroy infectivity of all of the viruses tested so far, giving us a

TABLE 2.—*Properties of Hepatitis B Surface Antigen (HBsAg) Derived From Human Plasma*

HBsAg in HBeAg+ plasma	500.0 mg/liter
HBsAg in anti-HBe+ plasma	50.0 mg/liter
Half-life in humans	3.3 days
Excretion of catabolized HBsAg in urine	25.0 mg/day
Common antigenic determinants most immunogenic in humans	a (subtypes a_1, a_2^1, a_2^3, a_3), Re
Other antigenic determinants poorly immunogenic in humans	d/y, w/r, g, j, k, q, t and x
Composition of viral envelope purified from plasma	
Lipids	22.5%
Carbohydrates	7.5%
Proteins	70.0%
Polypeptide P1	25,000 daltons
Polypeptide P2 (glycosylated P1)	29,000 daltons
Polypeptide P6 (albumin+HBsAg)	68,000 daltons

HBeAg+ = hepatitis B e antigen-positive, anti-HBe+ = positive for antibody to HBeAg

strong assurance that no transmissible agent possibly present in human plasma could escape these inactivation procedures. Most important, there is no evidence whatsoever to suggest that the transmissible agent(s) of the so-called acquired immune deficiency syndrome (AIDS) escapes the inactivation procedures used in producing the vaccine.

The perinatal transmission of viral hepatitis type B can be prevented in 75% of the babies by hepatitis B immune globulin (HBIG) given at birth, within the first 24 hours and at intervals of one to three months for the first year of life.[37] Because infants and babies responded very well to the hepatitis B vaccine trials conducted in Africa, Asia and Europe, several clinical trials are now in progress to evaluate the efficacy of hepatitis B immune globulin and hepatitis B vaccine in passive-active immunization of high-risk neonates born to HBeAg-positive carrier mothers. The results of these studies promise a means of controlling propagation of the chronic carrier state. It is currently recommended that all babies born to chronic carriers of HBsAg should receive 0.5 ml of hepatitis B immune globulin within the first 24 hours, followed by vaccination with 0.5 ml of Heptavax-B (Merck Sharp & Dohme) at age 1 to 7 days, 1 month and 6 months.

Findings of the epidemiologic surveys by the Centers for Disease Control indicate that about 200,000 cases of hepatitis B virus infection occur each year in the United States. Acute hepatitis with jaundice develops in about 50,000 people, and 12,000 to 20,000 become carriers of the virus. Chronic hepatitis B is estimated to cause 4,000 deaths due to cirrhosis and 800 deaths due to hepatocellular carcinoma per year. At least 750,000 Americans and 200 million persons in the world are estimated to be carriers of HBsAg and serve as an epidemiologic reservoir of viral hepatitis type B. The vaccines containing HBsAg provide a real hope of controlling this problem in the United States and worldwide. The major constraints still are availability and high cost for the population needing the vaccine most—that is, Asia and Africa.

An HBsAg carrier's plasma is a unique resource for large-scale production of the vaccine. The immunochemical characteristics of HBsAg are summarized in Table 2. Because the plasma of the most infectious donors, those who are HBeAg-positive, often contains the highest amount of HBsAg, it is the best resource for isolating HBsAg. Because the turnover rates are rapid (3.3 days), carriers can be repeatedly plasmapheresed to obtain a sustained supply of carrier plasma. The safety and efficacy of current hepatitis B vaccines render the attempts to make vaccines of component polypeptides of HBsAg less practical and unattractive.

The cost of screening donors, selecting suitable donors for plasmapheresis and processing the plasma for isolation of HBsAg increases the cost of the hepatitis B vaccines. Therefore, a second generation of technology to make HBsAg in vitro by recombinant DNA techniques or cell culture techniques is being actively pursued.[8,82-86] If these alternative means of producing HBsAg prove to be more economical than from plasma, a wider use of the vaccine is possible. Particularly in Africa and Asia, control of the perinatal transmission and chronic carrier state is urgently needed for worldwide strategies to control viral hepatitis B, chronic liver disease, hepatocellular carcinoma and δ-infection. Despite the fact that immunization against smallpox has been abandoned, in a recent re-

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  1   Met-Glu-Asn-Ile-Thr-Ser-Gly-Phe-Leu-Gly-Pro-Leu-Leu-Val-Leu-Gln-Ala-Gly-Phe-Phe-

 21   Leu-Leu-Thr-Arg-Ile-Leu-Thr-Ile-Pro-Gln-Ser-Leu(Asp-Ser-Trp-Trp-Thr-Ser-Leu-Asn-

                     Thr-Thr-                                        Thr-
 41   Phe-Leu-Gly-Gly-Ser-Pro-Val-Cys-Leu-Gly-Gln-Asn-Ser-Gln-Ser-Pro-Thr-Ser-Asn-His-
                     Thr-Thr-                                        Ile-
                                 Thr-
 61   Ser-Pro-Thr-Ser-Cys-Pro-Pro-Ile-Cys-Pro-Gly-Tyr-Arg-Trp)Met-Cys-Leu-Arg-Arg-Phe-
                                 Thr-

 81   Ile-Ile-Phe-Leu-Phe-Ile-Leu-Leu-Leu-Cys-Leu-Ile-Phe-Leu-Leu-Val-Leu-Leu-Asp-Tyr-

                                                     Ser-                    Pro-
101   Gln-Gly-Met-Leu-Pro-Val-Cys-Pro-Leu-Ile(Pro-Gly-Ser- Thr-Thr-Thr-Ser-Thr-Gly-Pro-
                                                     Ser-                    Ser-
          Arg-        Met-    Thr-            Thr-        Tyr-
121   Cys-Lys-Thr-Cys-Thr-Thr-Pro-Ala-Gln-Gly-Asn-Ser-Met-Phe-Pro-Ser-Cys-Cys-Cys-Thr-
          Arg-        Thr-    Pro-            Ile-        Tyr-
              Ser-                                                            Gly-
141   Lys-Pro-Thr-Asp-Gly-Asn-Cys-Thr-Cys-Ile-Pro-Ile-Pro-Ser-Ser-Trp)Ala-Phe-Ala-Lys-
              Ser-                                                            Gly-
      Phe-                        Ala-
161   Tyr-Leu-Trp-Glu-Trp-Ala-Ser-Val-Arg-Phe-Ser-Trp-Leu-Ser-Leu-Leu-Val-Pro-Phe-Val-
      Phe-                        Ala-
                                      Thr-                Val-
181   Gln-Trp-Phe-Val-Gly-Leu-Ser-Pro-Thr-Val-Trp-Leu-Ser-Ala-Ile-Trp-Met-Met-Trp-Tyr-
                                      Ile-                Val-
                                      Leu-
201   Trp-Gly-Pro-Ser-Leu-Tyr-Ser-Ile-Val-Ser-Pro-Phe-Ile-Pro-Leu-Leu-Pro-Ile-Phe-Phe-
                                      Leu-
                  Val-
221   Cys-Leu-Trp-Val-Tyr-Ile.
                  Ala-
```

Figure 5—The amino acid sequence derived from the nucleotide sequence of the gene S. The sequence corresponds to the HBsAg/*adw* subtype with substitutions in the *ayw* indicated above and those in the *adyw* complex subtype indicated below the central sequence.[8] One of the two hydrophilic regions between residues 110 and 156 has been shown to contain the major antigenic specificities.[88] The *a* determinant common to all serotypes is determined by a minimum sequence of 139 to 147 residues,[90] whereas the d/y specificities are determined by a minimum sequence of 125 to 137 residues.[93] A disulfide-cyclized peptide of sequence 122 to 137 possibly contains an additional *a* specificity.[94] One or more of the synthetic peptide analogues corresponding to the specificity of a physiologic immune response in humans could be a candidate vaccine.

port of a highly immunogenic vaccine a vaccinia virus-HBsAg gene recombinant hybrid was used.[87] This recombinant live virus may prove most useful in neonatal immunization in Asia, Africa and Latin America.

The amino acid sequence of the envelope protein has provided an opportunity to synthesize peptide analogues of HBsAg.[88-93] Within the hydrophilic region of residues 110 to 156 (Figure 5),[8] the d/y determinants are specified by amino acid residues 110 to 137.[94] Amino acid residues 139 to 147 specify the *a* determinant common to all serotypes of HBsAg.[90] The heterogeneity of HBsAg/*a* determinant, shown in Table 2, allows for the possibility that a portion of the *a* specificity may be determined by the disulfide-dependent conformation of a cyclic peptide analogue of residues 122 to 137 of the amino acid sequence.[95]

The alternative of synthetic peptides vaccine is possibly more attractive than other forms of HBsAg because of its possible application in terminating the chronic carrier state. Not only can a dimeric form of HBsAg peptide analogues coupled with tetanus toxoid serve as a vaccine, but it can conceivably be used in terminating the chronic carrier state by overcoming a specific immunologic tolerance to the *a* determinant of HBsAg.[15,96] A safe and effective outcome of this pursuit may bring to fruition the purpose of our decade-long investigations on the molecular immunology of HBsAg.

In summary, prevention is better than cure, and the available vaccine or its future substitutes may ultimately lead to the elimination of hepatitis B virus infection along with its companion δ-agent, of chronic liver disease and of the development of hepatocellular carcinoma.

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Medical Staff Conference

Paget's Disease of Bone

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Internists have long been interested in Paget's disease of bone, which has traditionally been considered a common metabolic bone disease despite its localized nature. Unfortunately, however, there was little that could be done therapeutically for that subgroup of patients with extensive disease or with pain. Fortunately that lack of a therapeutic approach to Paget's disease has changed. Dr Gordon Strewler from the Endocrine Division of the Veterans Administration Medical Center will bring us up to date concerning these developments.*

DR STREWLER:† Paget's disease of bone (osteitis deformans) is a common, sometimes crippling, disorder. Although our understanding of its etiology and pathogenesis is still incomplete, advances of the past 15 years have revolutionized its therapy.[1-3] I will review the clinical features of Paget's disease, the indications for therapy and the new treatments that are now available.

Clinical Features

James Paget reported the first cases of osteitis deformans in 1877, and later summarized its features: "It begins in middle age and later, is very slow in progress, may continue for many years without influence on the general health and may give no other trouble than those which are due to the changes in shape, size and direction of the diseased bones. Even when the skull is hugely thickened and all its bones exceedingly altered in structure, the mind remains unaffected."[4(p6)] In 1984 we can enlarge on this succinct description chiefly by adding that a localized, disorganized increase in osteoclastic bone resorption seems to be the primary event in Paget's disease. This is manifested systemically by an increase in the urinary excretion of hydroxyproline, a product of the collagen degradation that occurs as bone matrix is resorbed. Bone formation is increased secondarily, manifested by increased release of alkaline phosphatase into serum from active osteoblasts. Locally, resorption or formation typically predominates, producing bone lysis or sclerosis, respectively. From a systemic point of view, however, resorption and formation of bone remain well coupled in Paget's disease, as indicated by the correlation between urinary hydroxyproline and serum alkaline phosphatase values in individual patients (Figure 1).[5] It follows that either of these can be used to monitor activity of the disease.

Active Paget's disease is characterized histologically by highly cellular bone in which the normal lamellar pattern is replaced by a mosaic of microscopic foci of new bone, joined by prominent cement lines. Osteoclasts are present in large numbers, and some have intranuclear and cytoplasmic inclusions that resemble the nucleocapsids of paramyxoviruses.[6,7] From this important observation has arisen speculation that Paget's could be a slow viral disease; however, as attractive as this proposal is in explaining the sporadic and spotty character of the disorder, we have yet to substantiate it by fulfilling Koch's postulates for an infectious cause.

As Paget noted, osteitis deformans is usually symptomatic in middle-aged and elderly persons. Its prevalence in persons older than 40 years is about 3%, in both autopsy and radiologic surveys, and men and women are affected equally.[8] It is important to note that no more than 10% to 20% of patients with Paget's disease identified in populational x-ray surveys have symptoms (bone pain, deformity or fractures). No method exists at present to identify a subpopulation of such patients who are at risk for pain.

Paget's disease can be detected readily by x-ray film or, when active, by isotopic bone scans. It can involve any bone but has a predilection for the axial skeleton.

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†Gordon J. Strewler, MD, Assistant Professor of Medicine, Department of Medicine, VAMC and University of California, San Francisco.

(Strewler GJ: Paget's disease of bone—Medical Staff Conference, University of California, San Francisco. West J Med 1984 May; 140:763-768)

The commonest sites are the sacrum and spine (50% of patients), femurs (46%), skull (28%), sternum (23%) and pelvis (22%).[9] Paget's disease often begins as a lytic lesion of bone.[10] Typical in the long bones is a flame-shaped front of advancing osteolysis (Figure 2, left). Subsequently, reactive sclerosis may produce the common mixed pattern, in which coarse trabeculae and cortical thickening are also present (Figure 3), or it may produce a predominantly sclerotic form of Paget's disease. The bony deformities of Paget's disease (osteitis deformans) are due to *abnormal remodeling* of weight-bearing bones—that is, tibial bowing, basilar impression (platybasia)—or to *enlargement* (Figure 3, ischial ramus). Enlargement of bones is rarely seen in other disorders, such as osteoblastic metastasis, that may otherwise mimic Paget's disease radiographically.

The complications of Paget's disease may be grouped into the following four categories (Table 1).

Complications of Paget's Disease

Rheumatologic. Commonly present in patients with Paget's disease, osteoarthritis may be an incidental finding or may result from abnormal stresses due to the softening and deformity of pagetic bone (Figure 3). Paget himself noted an association between osteitis deformans and gout, and a correspondingly high incidence of hyperuricemia has recently been found.[11] Rheumatoid arthritis, ankylosing spondylitis and calcific periarthritis are also common.[11] Arthritis often presents a conundrum to a clinician attempting to relieve a patient's pain, as it may be difficult to determine whether the pain originates in pagetic bone or in the nearby joint (see below, Indications for Therapy).

Neurologic. The brain, spinal cord and peripheral nerves are all at risk for involvement in Paget's disease.[12] In patients with skull involvement, softening and inward collapse of the base of the skull may precipitate basilar impression (platybasia), with symptoms of brain-stem or spinal cord compression, obstructive hydrocephalus or vertebrobasilar vascular insufficiency. Much more common is cranial nerve dysfunction. Deafness of the sensorineural type occurs in up to 50% of patients with skull involvement, apparently as the result of cochlear damage, and any of the other cranial nerves may be entrapped. The spinal cord and roots are subject to impingement as the result of bone encroachment, vascular insufficiency or vertebral collapse (unlike osteoporotic vertebrae, pagetic ones frequently expand circumferentially as they collapse, perhaps because of a relatively greater trabecular bone mass). Peripheral nerve entrapment can produce carpal or tarsal tunnel syndromes.

Metabolic. Despite sometimes greatly increased turnover of bone, extracellular calcium metabolism is relatively normal—a tribute to precise coupling of bone formation and resorption. However, during immobili-

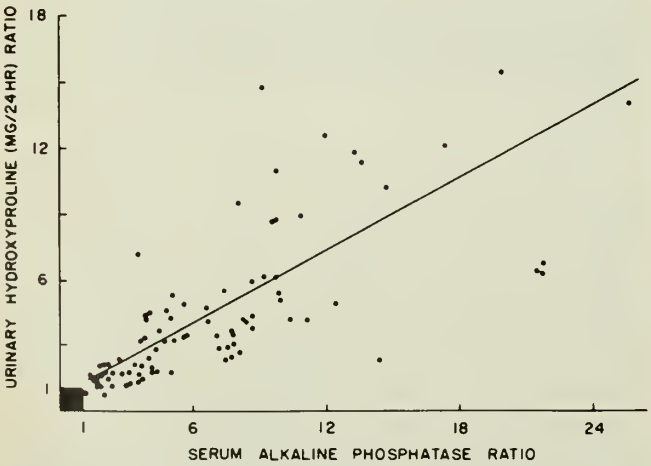

Figure 1.—Serum alkaline phosphatase and urinary hydroxyproline levels in 89 patients with Paget's disease. Both are plotted as the ratio of a patient's value to the upper limit of normal (normal range, black square). Alkaline phosphatase and hydroxyproline are correlated ($r = .66$, $P < .01$). (Reprinted with permission from Canfield et al.[5])

Figure 2.—Lytic Paget's disease in the tibia before **(left)** and after **(right)** immobilization in a cast. The lytic area has a flame- or V-shaped leading edge **(left)**.

zation a patient who has Paget's disease is prone, as are normal persons, to a net increase in bone resorption. Locally, this may manifest as rapid osteolysis (Figure 2); systemically, hypercalciuria and hypercalcemia may result, as they do from immobilization in other states of high bone turnover, such as thyrotoxicosis and normal childhood development. The incidence of urinary calculi in cases of Paget's disease is at least 5%,[13] but the details of their pathogenesis are unknown; it is likely that only a few are attributable to episodic hypercalciuria.

Neoplastic. The most terrible complication of Paget's disease is the development of bone sarcoma. The tumor arises in pagetic bone, characteristically in patients who have polyostotic involvement. Although bone sarcomas typically are tumors of young people, they are estimated to occur in about 1% of patients with Paget's disease and up to 10% of patients with extensive involvement. Consequently, fully 30% of elderly patients with osteosarcoma suffer from Paget's disease.[14] Osteosarcoma is most common, but fibrosarcoma, giant cell tumors and chondrosarcoma also occur. These tumors usually present with swelling and increased pain. Radiologically, they are often destructive lesions, with interruption of the cortex (Figure 3).

Figure 3.—Paget's disease in the right femur and pelvis. The right femur displays cortical thickening and coarse trabeculation. The right ischium is enlarged, with sclerosis of ischiatic and pubic rami and right ilium. Two complications of Paget's disease are present. There is concentric, bilateral narrowing of the hip joint space, signifying osteoarthritis. The destructive lesion interrupting the cortex of the right ilium is an osteosarcoma.

TABLE 1.—*Complications of Paget's Disease*

Rheumatologic
Osteoarthritis
Gout
Calcific periarthritis
Rheumatoid arthritis
Neurologic
Basilar impression
Cranial nerve dysfunction (especially deafness)
Spinal cord and root compression
Peripheral nerve entrapment (carpal and tarsal tunnel syndromes)
Metabolic
Immobilization hypercalciuria/hypercalcemia
Urolithiasis
Neoplastic
Bone sarcoma
Giant cell tumor

Treatment

It was stated at the outset that Paget's disease is a primary disorder of osteoclast function. This construction of its pathogenesis predicts—and recent data have mostly confirmed—that inhibition of osteoclastic bone resorption could ameliorate the entire clinical syndrome. After a century of frustration in treating Paget's disease, three specific forms of therapy are now available: calcitonin, the diphosphonates and mithramycin. Each is the culmination of a long trail of investigation, which was directed towards Paget's disease only in its latter stages, and the three have in common only one feature, inhibition of the osteoclast.

Calcitonin

Calcitonin is a 32-amino-acid peptide hormone secreted by the parafollicular C cells of mammalian thyroid.[15] Its chief biologic effect is inhibition of osteoclastic bone resorption, and in states of high bone turnover (such as Paget's disease), it can produce hypocalcemia. It is unclear whether calcitonin has a physiologic role as a calcium-regulating hormone in humans; neither thyroidectomy nor the substantial hypercalcitonemia associated with medullary thyroid carcinoma perceptibly alters extracellular calcium homeostasis. However, in pharmacologic doses the inhibitory effect of calcitonin on its principal target cell, the osteoclast, has proved useful in the treatment of Paget's disease.

The only form of calcitonin generally available in the United States is synthetic salmon calcitonin (Calcimar, USV Pharmaceutical). Synthetic porcine and human calcitonin have also been used in the treatment of Paget's disease, and they have similar effects. However, salmon calcitonin is considerably more potent in humans than are the mammalian hormones, including human calcitonin; hence, the cost of therapy is considerably less. (It seems illogical that the human calcitonin receptor would recognize the hormone of a fish so much better than its own, but the high potency of salmon calcitonin has been shown in direct measurements of binding to the mammalian receptor.[16]) Because the amino acid sequences of human and salmon calcitonin differ at 16 of 32 positions, salmon calcitonin is immunogenic in humans; antibody-mediated resistance, however, is fortunately rare.[17]

Calcitonin treatment of Paget's disease is typically initiated with a dose of 100 Medical Research Council (MRC) units a day, administered subcutaneously. In

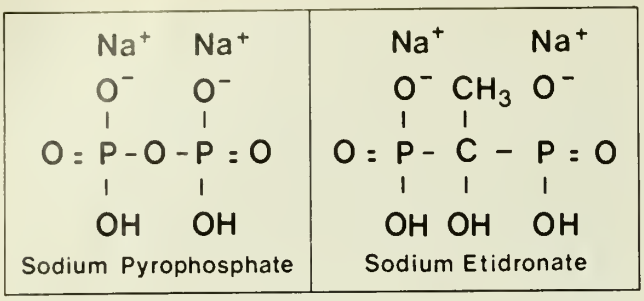

Figure 4.—Structures of pyrophosphate and etidronate. (Reprinted with permission from Wallach.[3])

long-term studies a dose of 50 MRC units three times a week has been shown to produce excellent results,[18] and most patients should be changed to this lower dose once a response has been obtained (one to two months). The optimum duration of therapy has not been defined, but most patients will continue in symptomatic and biochemical remission for several months after therapy is halted[19] and this encourages the use of intermittent treatment regimens.

It is estimated that 80% of patients will respond to calcitonin with significantly decreased pain. Although the placebo effect in Paget's disease is substantial—30% of patients have a symptomatic response to placebo[20]—there can be little doubt, even without a controlled clinical trial, that calcitonin is effective. Objectively, there is a fall in serum alkaline phosphatase and urinary hydroxyproline levels. Typically, both stabilize after two to three months at a third to half their pretreatment values; the explanation for this "plateau response" remains obscure. An objective response to calcitonin can also be detected using bone scintigraphy.[21] Improvement can frequently be documented on serial x-ray films if close attention has been paid to reproducible radiographic technique,[22] but the varying techniques used in taking routine films sometimes obscure these differences. Besides healing of lytic areas, an improvement in remodeling sometimes occurs, with restoration of normal corticomedullary junctions and decreased diameter of affected bones.[22] This observation is important, as it indicates that calcitonin, in addition to relieving symptoms, may alter the natural history of pagetic bone disease. The effect may not be shared by the available diphosphonate compound, etidronate disodium.

Calcitonin therapy is apparently safe. The major side effects are nausea and flushing following injection of the drug; both may be transient, disappearing with continued therapy. Mild hypocalcemia may be induced, but it is asymptomatic and, presumably because it is transient, does not stimulate progressive secondary hyperparathyroidism.

Etidronate

The diphosphonates, of which etidronate disodium (disodium ethane-l-hydroxy-l,l-diphosphonate [EHDP]) is one, were synthesized as analogues of inorganic pyrophosphate (Figure 3). Pyrophosphate has the potentially useful property of binding to hydroxyapatite crystals in bone and inhibiting their formation and dissolution, but is labile in vivo due to rapid hydrolysis by pyrophosphatases. The substitution of a carbon for the central oxygen of pyrophosphate produced the diphosphonates (Figure 4), which proved to be stable and effective as inhibitors of bone resorption.[23] Although their mechanism of action is incompletely understood, it appears to involve their ingestion by osteoclasts[23] rather than a physicochemical effect on extracellular hydroxyapatite.

Several diphosphonates have proved to be useful clinically, but only etidronate disodium (Didronel, Procter & Gamble) is available in the United States. Unlike calcitonin, the clinical effectiveness of etidronate has been verified in two double-blind studies of Paget's disease.[5,20] In both there were dose-related lessening of pain and improvement in biochemical indices with doses of 5 to 20 mg per kg of body weight a day. Notable was the 30% response of pain to placebo[20] that was commented on earlier. After administration of etidronate was stopped, a prolonged remission of symptoms and biochemical indices continued for up to a year in most patients.[5,24] In addition to the fall in serum alkaline phosphatase and urinary hydroxyproline levels, improvement can be seen on bone scans.[5,21]

An important adverse effect of etidronate is inhibition of bone mineralization, manifest as a dose-dependent increase in the width of osteoid seams.[25,26] This effect is apparently not shared by two other diphosphonate drugs that have been used clinically: dichloromethane diphosphonate and 3-amino-l-hydroxypropane-l,l-diphosphonate (APD).[26] Does the inhibition of bone mineralization by etidronate have adverse clinical effects? A disturbingly high incidence of pathologic fractures through pagetic bone has been reported in patients treated with etidronate,[26] but the incidence of such fractures in untreated patients is not known. Concern has been expressed that the fractures in treated patients could be related to poor mechanical stability of undermineralized bone. Also, careful studies of serial x-ray films of bone do not show healing of pagetic lesions as is seen with calcitonin; in fact, lytic lesions have progressed in some patients.[27] Finally, some patients treated with etidronate (10 to 20 mg per kg per day) experience *increased* bone pain.[5,26]

Based on these data, it is currently recommended that patients with Paget's disease be treated with no more than 5 mg per kg a day of etidronate for no longer than six months. Patients can be re-treated after they have been off therapy for six months. At this dose osteoid seam width is not increased, though the calcification rate of bone is substantially decreased.[25] There is no evidence of an increased fracture rate with this dose and duration of therapy,[24] and the biochemical response to etidronate (5 mg per kg a day) and calcitonin is similar. With these strictures, etidronate

TABLE 2.—*Indications for Therapy*

Accepted
Bone pain (unresponsive to anti-inflammatory agents)
Proposed
Preparation for surgical treatment
Immobilization
Calcium urolithiasis
Neurologic complications

therapy appears to be as safe and efficacious as calcitonin.

Mithramycin

Mithramycin is a cytotoxic antibiotic with an affinity for the osteoclast. Like calcitonin and etidronate, it is used for treatment of hypercalcemia in malignancy. Ryan and others have explored the use of short courses of mithramycin (10 to 25 μg per kg a day) for Paget's disease.[28] The clinical responses have been profound and often prolonged, but the agent's considerable toxicity to the liver, kidney and bone marrow mandate its use only in unusual circumstances and after the other available drugs have failed.

Indications for Therapy

Some proposed indications for treatment of Paget's disease are listed in Table 2. The only generally accepted indication for therapy is pain. However, not all patients with pain are candidates for specific therapy with calcitonin or diphosphonates. As previously mentioned, Paget's disease is often asymptomatic, and rheumatologic disorders are common in patients with this disorder. The pain in those persons who respond to nonsteroidal anti-inflammatory drugs may not be directly attributable to Paget's disease. Determining whether a patient's pain persists at night may also be helpful in making this judgment, since pagetic pain is often unremitting, while the pain of osteoarthritis is relieved by rest. The other indications for therapy in Table 2 are supported only by theory or anecdotal data.

For many patients, considerations of economics or acceptability may be decisive in choosing between calcitonin and etidronate for treatment of pagetic pain. The cost of etidronate treatment is about half that of calcitonin in the usual maintenance dose (50 MRC units three times a week), and some patients cannot tolerate injecting themselves with calcitonin. In certain specific circumstances, however, calcitonin may be the therapy of choice.

Based on the observed inhibition of bone calcification by etidronate, calcitonin seems the better drug on theoretic grounds for patients with healing fractures and those undergoing an orthopedic operation. There are presently no data to support this view, however. Calcitonin has been proposed as a preoperative therapy to reduce bleeding during an orthopedic surgical procedure and to enhance healing, but there is only anecdotal evidence that these salutary prophylactic effects occur. For the most part, pagetic bone heals well without specific treatment, but there is an increased incidence of nonunion of fractures through pagetic bone.[4]

Calcitonin seems preferable to etidronate in persons whose bone is threatened by an advancing lytic lesion, with the possibility of impending fracture, because available data[22] suggest that it promotes healing of such lytic areas. Calcitonin has also been advocated in immobilization to avoid local bone lysis (Figure 2) as well as hypercalciuria and hypercalcemia. Because immobilization hypercalcemia is actually quite uncommon in cases of Paget's disease, therapy in this instance should be directed at reversal of documented abnormalities (advancing lytic areas, hypercalcemia, pronounced hypercalciuria or calcium urolithiasis), rather than prophylaxis.

The neurologic complications of Paget's disease may respond to calcitonin therapy. The most responsive lesion, according to published case data, seems to be transverse myelopathy from spinal cord compression.[12] A trial of medical therapy with calcitonin may be warranted in many patients with progressive neurologic lesions; if unsuccessful in reversing the neurologic deficit, the treatment will serve to prepare the patient for a decompressive procedure. Calcitonin is advocated because clinicians have had more experience with it in these cases; etidronate may prove to be equally useful.

Perspectives

As the preceding section shows, despite remarkable progress in the treatment of Paget's disease over the past 15 years, our ignorance is still considerable. Would calcitonin and etidronate, with distinct mechanisms of action on the osteoclast and different toxicities, be useful in combination? Combination therapy has been used successfully[29] but has not been compared in a controlled study with the effects of either drug by itself. What should be the indications for medical treatment of the complications of Paget's disease? Should asymptomatic persons with advancing lytic lesions be treated prophylactically? Should all patients with extensive disease (more than 50% of the skeleton involved) be treated to lessen the risk of malignant degeneration, which is estimated at 10% in this group? As these questions show, the treatment of Paget's disease is in its infancy, and there is still much to learn.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

In Vitro Fertilization

QUESTION:

Is in vitro fertilization considered investigational or accepted medical practice at this time?

OPINION:

In the opinion of the Scientific Advisory Panel on Obstetrics and Gynecology, in vitro fertilization can be considered accepted clinical practice under selected circumstances. The complexity of the procedure is such that it should be done only in centers with rigid laboratory control by physicians expert in the technique. The number of such centers at present is limited.

As the technique and the indications for its use are not yet standardized, in vitro fertilization is not approved for use by all practitioners. Because advances in the field of in vitro fertilization are rapid, this question merits review periodically.

Epitomes

Important Advances in Clinical Medicine

Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in neurosurgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 44 Gough Street, San Francisco, CA 94103

Management of Intraventricular Hemorrhage in Neonates

INTRAVENTRICULAR HEMORRHAGE can occur in any neonate but premature infants are at greatest risk as the fetal brain contains a subependymal germinal matrix, a gelatinous structure that overlies the caudate nucleus and is separated from the the ventricular system by only a single layer of ependymal cells. At term the matrix is but a remnant whereas in premature infants this structure is large. Intracranial hemorrhage is usually preceded by a hypoxic-ischemic insult and may be followed by destruction of neuronal and glial precursors in the germinal matrix, destruction of brain parenchyma and hydrocephalus to a varying degree, depending on the magnitude of the hemorrhage. The immediate management of a neonate with intracranial hemorrhage is directed toward maintaining adequate cerebral perfusion and preventing conditions that might lead to further extension of the hemorrhage—such as arterial hypertension, hypoxemia, hypercapnia, acidemia and rapid changes in blood volume and osmolality. Neurosurgical treatment is limited to the hydrocephalus. The effectiveness of various methods of treating hydrocephalus is somewhat unclear because, with relatively the same amount of blood in the ventricles and subarachnoid spaces, the hydrocephalus will resolve on its own in some cases where it will progress in others.

The initial treatment of posthemorrhagic hydrocephalus is with repeated lumbar puncture. If the hemorrhage produces obstruction between cerebrospinal fluid in the ventricles and that in the lumbar region, lumbar punctures will be ineffective and it will be necessary to control the hydrocephalus by removing fluid directly from the ventricles. One way to accomplish this is with repeated ventricular taps but at the expense of additive parenchymal damage. An alternative procedure is to insert a ventriculostomy, which allows cerebrospinal fluid to continuously drain externally. This method obviates the need for multiple ventricular punctures but can be cumbersome, require particular attention to detail in its management and be complicated by infection, obstruction and dislodgement.

Another approach is to place a subcutaneous ventricular catheter reservoir that can be intermittently tapped percutaneously to remove cerebrospinal fluid. The design of smaller, more pliable reservoirs has eliminated the problems of skin or wound breakdown for even the smallest of premature infants. The reservoir can be aspirated daily for months without infection. Obstruction of the reservoir has not proved to be a problem in spite of the fact that the fluid can be very bloody and has a high protein content. The reservoir is very rarely tapped more than once a day, the hydrocephalus being controlled instead by increasing the amount of cerebrospinal fluid aspirated at each tap. The major drawback to using the reservoir is that the removal of fluid is intermittent. It is not known whether the fluid buildup and concomitant rise in intracranial pressure between taps are detrimental; clinical experience indicates that this is not a significant factor. If the hydrocephalus does not resolve, the reservoir can be converted to a ventriculoperitoneal shunt without a valve as an elective procedure.

Apparently the outcome of infants who have intraventricular hemorrhage depends more on the degree of intraparenchymal hematoma than the extent of the

ventricular clot or the degree of the ensuing hydrocephalus. Fortunately, a precipitous decline in the prevalence of severe intraventricular hemorrhage in preterm infants has been noted, the reasons for which are yet to be fully determined. J. GORDON McCOMB, MD

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Central Nervous System *Taenia solium* Infestation (Cysticercosis)

MIGRATION OF PERSONS from endemic areas is increasing the frequency with which central nervous system signs of infestation of the larvae of *Taenia solium* are encountered. Well-recognized manifestations include diffuse parenchymatous disease; calcified larval forms causing seizures; a basilar adhesive and racemose form, ventriculitis; intraparenchymatous disease with the formation of mass (cystic) lesions; intraventricular cysts, and spinal forms of both an inflammatory and a mass nature. The clinical manifestations include toxic encephalopathy with increased intracranial pressure, a focal neurologic deficit from intraparenchymatous disease, obstructive hydrocephalus from intraventricular disease or adhesive processes in the cerebrospinal fluid pathways, meningitis and spinal cord compression. These features may occur singly or in combination. Diagnosis is based on probable epidemiologic exposure, historical and physical findings, radiologic studies—specifically, computed tomographic (CT) investigation—and serologic examination. Palliative surgical therapy is appropriate for the relief of hydrocephalus when this is produced by ventriculitis or an obliterative inflammatory process involving the apertures of the ventricular system or the basilar cisterns (or both) and rarely for the excision of mass lesions when they present as focally dangerous mass processes. Surgical "cure" of intraventricular cysts may be expected if these are the only manifestations of central nervous system disease and if all such lesions are removed. This requires direct access to the cysts, which may be encountered—singly or otherwise—in the lateral, third or fourth ventricle.

Recent advances in our understanding relate to the recognition of more limited clinical syndromes produced by the death of intraparenchymatous larval forms. Such involution is presumably due either to the natural immunocompetence of the body or to the use of pharmacologic agents, or both. The progress of focal intraparenchymatous disease can now be observed by sequential CT scan study and shows a feature of the infestation not heretofore generally recognized. Thus, in contrast to the often overwhelming manifestations of diffuse parenchymatous involvement, the same inflammatory process, but of a more limited and localized kind, is being observed. Clinically and radiologically this process progresses to death of the larvae with establishment of the calcified state and with a quieting of the severe antigenic response (probably akin to a Jarisch-Herxheimer reaction). Whereas the control of such acute inflammatory features may be achieved with steroid therapy, recurrence often occurs unless larvacidal drugs are used. The derivative of pyrazinoisoquinoline (praziquantel) is now being applied in Mexico, South America and sporadically in the United States. The drug is of low toxicity and in incompletely "controlled" clinical experience is reported to be sufficiently promising to urge its use for almost all forms except strictly intraventricular cystic disease or masses causing spinal cord compression. Surgical palliative treatment for other causes of hydrocephalus may still be required. W. EUGENE STERN, MD

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Computed Tomography of the Spine

X-RAY COMPUTED TOMOGRAPHY (CT) has become the most useful tool for diagnosing spinal, intraspinal and paraspinal pathologic conditions. The technically advanced equipment rapidly generates highly detailed images of bone and soft tissue, enabling a multitude of uses in congenital, traumatic, inflammatory, neoplastic and degenerative diseases.

With complex spinal deformities or extensive tumors, in addition to the primary axial images, secondary images reformatted in coronal, sagittal or oblique planes are often useful. Reformatted images are also used when scan sections must be obtained oblique to the axis of interest.

Injecting the myelographic contrast agent, metrizamide, into the cerebrospinal fluid continues to add new dimensions to CT. This water-soluble, nonionic, radiodense agent, used in CT in volumes and concentrations much lower than those necessary for plain-film metrizamide myelography, defines the subarachnoid space, fills root sleeves, outlines the cord, conus, roots and cauda and fills the hydrosyringomyelic cavity. Metrizamide CT is often used as an adjunct to plain-film metrizamide myelography and in many instances replaces it.

The smaller doses of metrizamide CT produce significantly less morbidity, and newer agents with even fewer side effects are being developed. Low-dose metrizamide CT is gaining acceptance as an outpatient procedure.

In lumbar spondylosis and disc rupture, CT without the use of a contrast medium often produces diagnostic studies with more useful information than from conventional myelography; in many instances a surgical procedure for disc rupture or spinal stenosis is done on

the basis of a CT diagnosis without myelography.

CT is routinely used in postlumbar disc operations (failed back surgery syndrome). Computed tomography is valuable in defining bony stenosis of the spinal canal, lateral recess or a neural foramen; however, differentiating between recurrent disc herniation and epidural scarring may be difficult and is controversial. Metrizamide definition of the subarachnoid space and root sleeves may help.

Intravenous administration of contrast media has limited usefulness. It may enhance visualization of epidural scar tissue and intraspinal tumors.

Nuclear magnetic resonance CT has proved valuable in the diagnosis of hydrosyringomyelia, spinal tumors and gross pathologic conditions of the cord, but at the current stage of development it is much less useful than x-ray CT in diagnosing most other spinal pathology.

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Metastatic Tumors of the Spine

SYMPTOMATIC METASTATIC lesions of the spine develop in up to 14% of patients with malignant tumors. Such tumors most frequently arise in the lung, prostate, breast, kidney and thyroid and from lymphomas and multiple myeloma. The major presenting symptoms are spinal or radicular pain (or both), motor weakness, sensory loss and loss of sphincter control. Studies useful in establishing the diagnosis include plain spine x-ray films, radionuclide bone scanning, computed tomography and myelography.

For spinal metastasis limited to bone and producing only pain, radiotherapy and, where appropriate, chemotherapy constitute the treatment of choice. For lesions in the epidural space producing spinal cord compression, treatment is controversial. Traditionally these lesions have been treated with decompressive laminectomy followed by radiotherapy. Some recent reports suggest, however, that radiotherapy alone may be as effective as the combination of laminectomy and radiotherapy. High-dose systemic corticosteroids may produce dramatic relief of symptoms and are recommended for patients undergoing either irradiation or laminectomy.

A recent advance in the treatment of spinal epidural metastatic tumors involves resecting the vertebral body anteriorly and replacing it with acrylic. This approach often provides better tumor removal and spinal decompression than laminectomy because metastatic spinal lesions compressing the spinal cord or cauda equina often originate in the vertebral body and grow posteriorly. Anterior vertebral body resection and acrylic replacement also provide spinal stability rather than contributing to instability, as in the case of laminectomy.

Regardless of the form of therapy all authors agree that results are best when neurologic deficits are mild. Patients known to have cancer who complain of spinal or radicular pain, leg weakness or numbness or sphincter dysfunction should be assumed to be suffering from spinal metastasis. Aggressive radiologic investigation and prompt therapy are essential to prevent paraplegia.

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Locked-In Syndrome and Coma Vigil

ONE OF HISTORY'S most prolific authors, Alexandre Dumas, described in his classic story *The Count of Monte Cristo* (1844) a man made helpless by a paralytic stroke whose sole means of communication with his relatives, friends and visitors was the blinking of his eyes. His may have been the first description of the "locked-in syndrome," given more recent attention by Plum and Posner, who suggested the term, and by other authors. These locked-in patients have lost, through destruction of descending pathways in the brain stem—usually by vascular, traumatic or progressive degenerative mechanisms—the ability to initiate speech or extremity motion, while retaining a fully alert and responsive conscious state. They, like the character of Dumas, are in fact the wakeful and thinking prisoners of their bodies. A recently recognized cause of a motionless, "frozen" state with normal consciousness is the severe parkinsonian picture produced by substantia nigra cell destruction by one of the products of street drug manufacture, MPTP (1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine).

By contrast, patients with akinetic mutism, or its French synonym, coma vigil, have a clinical picture consisting of an apparently alert state, with open eyes following an examiner but without communication. Such patients' seeming wakefulness is illusory, and examination shows the absence of any suggestion of consciousness and no semblance of communication. They are, in fact, in coma, usually caused by extensive bilateral cerebral disease of traumatic, toxic, anoxic or vascular nature.

Clearly, the patients whose "de-efferented" state consists of the inability to interact with their environment while retaining mental function require careful and compassionate attention. Because they often retain spontaneous voluntary ocular motion, they can communicate with their surrounding world, if their unique and tragic state is recognized. Mechanisms of communication based on coded signals have been devised,

and related approaches using sophisticated detection of fine ocular motion are in development. More direct systems based upon the detection of changing cortical electrical or blood-flow patterns may be predicted to be helpful in assuring return of some interaction with the intelligent world for these patients, but all such approaches will require the alert recognition of patients whose profound motor impairment causes an appearance of coma in the presence of a functioning but isolated mind.

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Laser Applications in Neurosurgery

THE USE OF LASERS (*l*ight *a*mplification by the *s*timulated *e*mission of *r*adiation) for neurosurgical procedures has gained increased acceptance over the past three years. Presently three laser sources are being used for neurosurgical procedures: the carbon dioxide (CO_2) laser; the argon (Ar) laser; and the neodymium-yttrium-aluminum-garnet (Nd:YAG) laser.

The major advantage of laser sources is gained when they are used with a micromanipulator (to reduce physiologic tremor) connected to the operating microscope. This allows increased precision, a very gentle removal of tissue with the absence of mechanical deformation and varying degrees of hemostasis depending on the specific laser source used.

Lasers are most useful when the following criteria are present: (1) firm, nonaspiratable tumor consistency; (2) the lesion is in a critical area or in the motor-speech area of the brain; (3) the lesion is moderately vascular, and (4) the approach is narrow and instruments partially obscure the operative field.

The CO_2 and Ar lasers have been used to greatest advantage in removing extra-axial tumors such as acoustic neuroma, meningioma and the like, especially those in critical areas. Adapted to stereotaxic frames, they have been used to remove deep-seated intra-axial lesions. Their use for intra- and extra-axial spinal lesions has been similiarly encouraging. The Nd:YAG laser has recently been used for removing moderately vascular tumors and vascular malformations. The recent development of an Nd:YAG micromanipulator will expand its applications to fine microsurgical procedures.

The Ar and CO_2 lasers have been used for neuroablative surgical procedures (such as those for dorsal root entry zone lesions, myelotomy, trigeminal tractotomy) and have decreased surgical morbidity. When the Ar laser is used to pump (stimulate) a dye laser, the red light produced has been used to activate a hematoporphyrin derivative to treat malignant neoplasms. The application of this therapy to brain tumors is under investigation at a few institutions such as the University of California at San Francisco, the Mayo Clinic and the University of Southern California.

Low-power, dedicated CO_2 lasers have been used to weld tissues—that is, to do microvascular and microneural anastomoses and tendon repair. Similar accomplishments have been achieved using the Ar and Nd:YAG lasers. Their clinical usefulness is under investigation.

Most recently lasers have been combined with fiberoptic endoscopes and angiographic catheters for vaporizing atherosclerosis in coronary and peripheral arterial vessels. The application of this new technology to cerebral vessels will be investigated in the near future.

In the next year, we will undoubtedly see new wavelengths introduced, each with its own specific application. Multilaser systems and the linking of lasers to computers for automated tissue removal, ultrasound depth-controlled lasers and new forms of delivery systems are potential advances. All of these innovations will increase the usefulness of lasers and improve our microneurosurgical techniques. Although the laser represents a technologic advance for neurosurgery, one must always keep in mind the adage "If you don't need a laser, don't use one."

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Spinal Infusion of Morphine for Pain

IT IS NOW FIVE YEARS since the first report appeared indicating that prolonged analgesia followed intrathecal morphine installation in cancer patients. This report was quickly followed by others relating the experience of analgesia with the epidural use of morphine and meperidine. These initial trials were based on earlier research—which has been reviewed—showing the action of spinal opiates at certain sites within the nervous system. The number of articles describing intraspinal narcotic use has rapidly expanded since these initial reports.

Postoperative pain has been treated with promising results; excellent and long-lasting relief of pain is provided and there is a concomitant reduction in the need for additional systemic analgesics. Significant advantages are conferred on a postoperative patient; analgesia is provided with a minimal narcotic effect, less central sedation occurs and pulmonary function is improved. Multiple side effects are known to occur, however, the most significant being possible respiratory depression. Monitoring of respiration for at least 24 hours following intraspinal narcotic administration, on an acute basis, is thus required.

Chronic pain syndromes have been treated in the same fashion; analgesia is unaccompanied by significant changes in motor function, sympathetic outflow or re-

sponse to nonnoxious stimuli and apparently the risk of respiratory depression is very low. Patients with various malignant conditions have benefited from this technique.

Implantable devices designed to deliver the narcotics have been used; tolerance to continuous intrathecal infusion of morphine, however, has been noted. The best candidates for this procedure appear to be those patients with intractable pain below the diaphragm of malignant origin. Patients should respond to a test dose of intrathecally given morphine with at least six hours of pain relief. An intraspinal morphine preparation has been approved by the Food and Drug Administration and implantable reservoirs for continuous infusions of morphine are available. In the future, selective spinal antinociception will expand to other spinal receptor populations as we move to an era characterized by the delivery of multiple selective spinal agonists and antagonists of the central nervous system.

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When Should Intracranial Pressure Monitoring Be Used?

INTRACRANIAL PRESSURE MONITORING remains controversial and is not used consistently by neurosurgeons. Despite lack of actual proof of improved outcome due solely to intracranial pressure control, intracranial pressure monitoring nonetheless has strong advocates who cite anecdotal evidence for the importance of these techniques in some disease states.

Intracranial hypertension (usually defined as a pressure of 20 or 25 mm of mercury or more) has been shown repeatedly to correlate adversely with poor outcome from head injury. Most patients with traumatic coma and hemorrhagic abnormalities on computed tomographic (CT) scans have intracranial pressure elevations, which should be monitored and controlled if possible. In such comatose patients with normal initial findings on CT scans, intracranial hypertension rarely develops within 24 hours of injury but delayed CT abnormalities can develop and intracranial pressure can rise after the first day. Thus pressure monitoring should be considered for patients who remain comatose and whose CT scan findings become abnormal.

Neurologic dysfunction in Reye's syndrome, once thought to be almost uniformly fatal, usually is attended by increased intracranial pressure. While some permanent neurologic damage or even death can still occur with this toxic hepatoencephalopathy, brain injury probably arises from ischemia due to intracranial hypertension and often can be avoided by intracranial pressure monitoring and control.

In recent years monitoring of intracranial pressure has been used in a variety of neurosurgical patients. For patients undergoing craniotomy for lesions such as arteriovenous malformations, aneurysms or brain tumors in which the surgeon feels postoperative brain swelling may occur, intracranial pressure monitoring offers an important guide to therapy directed at ensuring optimal cerebral perfusion. Ventriculomegaly from cerebrospinal fluid outflow obstruction by hemorrhage or tumor can be treated by ventriculostomy and drainage; intracranial pressure monitoring via an intraventricular catheter can determine the amount of drainage required as well as resolving need for drainage. Permanent cerebrospinal fluid shunting can be avoided by this technique in some patients.

Iatrogenic barbiturate coma has been advocated in some types of brain injury such as trauma or focal ischemia, though the efficacy of this therapy is not yet proved. Because most neurologic function is severely depressed with this treatment, intracranial pressure monitoring is advocated to ensure that a progressive intracranial pathologic condition such as brain swelling or hematoma formation is detected and treated so that adequate cerebral perfusion is maintained.

The treatment of increased intracranial pressure has been discussed in detail elsewhere. Because there is some toxicity involved with these therapies, they should be used as sparingly as possible to maintain normal intracranial pressure. There is poor correlation with changes in the intracranial pressure and alterations in the neurologic state; intracranial pressure elevations can be detected earliest and best by pressure monitoring. Using current low-risk techniques for monitoring intracranial pressure, proper therapy in appropriate amounts can be administered to ensure adequate brain perfusion.

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Computed Tomographic Guided Stereotaxis of the Brain

COMPUTED TOMOGRAPHIC (CT) imaging has enhanced the accuracy and safety of diagnosis and therapy in many provinces of medicine. The wedding of principles of stereotaxic neurosurgery and computed tomographic imaging has added an immediate new dimension to neurologic surgery and offers great potential for future innovation.

As opposed to CT-monitored techniques that commonly aid intracranial manipulation in the setting of a radiology suite, CT-guided stereotaxis allows selection of intracranial target points in a scanner, with minimal scan time (15 minutes or less). Target point data are

then sent to a neurosurgical operating room, where the intracranial procedure may be undertaken in an advantageously flexible and familar setting with regard to instrumentation, sterility and skilled neurosurgical nursing personnel.

Using these techniques, it is now possible under local anesthesia to have direct and accurate access (within 1 mm) to any intracranial point (cerebrum, cerebellum or brain stem) without the need for craniotomy and with recovery times of less than six hours. Absolute diagnosis may be obtained for suspicious lesions by techniques that use 4-mm scalp incisions, 3-mm twist drill calvarial perforation and miniature conduits and instruments at a target point. Biopsy and culture material taken by the use of these techniques provides histologic and microbiologic data that allow logical direction of subsequent therapeutic strategies and circumvent the often nebulous nature of radiographic assessment and the attendant risks of major craniotomy.

With this technique several instruments can be used at the intracranial target point to accomplish several objectives, including retrieving tissue, draining fluid collections, evacuating hematomas or abscess debris, placing therapeutic radionuclides and taking a biopsy or excising certain circumscribed lesions using a miniature cerebroscopic device.

The technique provides a totally new perspective and alternative in the management of intracranial mass lesions, which will increase in sophistication and capability with developments in image data processing, instrumentation at the target point and adaptation to nuclear magnetic resonance and positron emission tomographic imaging.

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Effects of Minor Head Injury

MINOR HEAD INJURIES account for the admission to hospital of about 400,000 patients annually in the United States; the number of patients briefly rendered unconscious and not admitted to hospital is unknown and therefore the total cohort of persons at risk to suffer the residue of a minor head injury substantially exceeds those requiring hospital treatment. Minor head injury may be defined as a history of unconsciousness not exceeding 20 minutes, a Glasgow Coma Score of 13 to 15 and a hospital stay for not more than 48 hours. A small but significant percentage of those persons have cognitive-behavioral deficits that primarily involve reduced attention-concentration, impaired complex information-processing skills, increased irritability and memory problems. Negligible cognitive-behavioral sequelae were once thought to accompany minor head injuries and most patients with such trauma are discharged from hospitals with normal neurologic signs after observation. Those who have headaches, increased anxiety, emotional lability, concentration deficits and memory problems after a minor head injury are often stated to suffer from a "postconcussive syndrome," a syndrome thought to represent a psychologic disturbance rather than damage to neural tissue induced by trauma. Evidence for psychogenic determinants is not lacking but recent histologic, neurophysiologic and neuropsychologic data point to specific neuropathologic alterations associated with postconcussive symptoms in cases of minor trauma.

A mechanism proposed to account for neural damage and behavioral dysfunction in minor head injuries is shear-strain. This model suggests that acceleration-deceleration injuries result in axonal tearing and neural degeneration. Because 80% of all minor head injuries are related to vehicular accidents, falls and sports injuries, a model of shear-strain emphasizing acceleration-deceleration and rotational forces seems especially relevant to minor head trauma. Minor head injury is a multifactorial disorder and the outcome is related to many factors. For now, it is essential to recognize that mild head injury is an overlooked condition that may result in neuropsychologic dysfunction that necessitates intensive evaluation and treatment.

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Chemonucleolysis

CHEMONUCLEOLYSIS REFERS TO intradiscal therapy for herniation of the nucleus pulposus using a proteolytic enzyme. The concept of chemical dissolution of a nucleus pulposus dates back to the early 1950s. Various enzymes have been proposed; however, the drug in current clinical use is chymopapain, a proteolytic enzyme derived from papaya latex, which has an affinity for acid mucopolysaccharide occurring in the nucleus pulposus. Chemonucleolysis was first attempted in human beings in 1963 following earlier animal experiments using chymopapain given intravenously to rabbits. The ensuing two decades were marked by considerable controversy and debate concerning the safety, effectiveness and toxicity of proteolytic enzymes in intradiscal therapy. Following prolonged double-blind studies, chymopapain achieved approval by the Food and Drug Administration for clinical usage in November 1982.

Stringent clinical criteria for patient selection must be observed. The following indications for chemonucleolysis have been recommended: documented herniated nucleus pulposus with nerve root involvement, significant disability resulting from pain, and failure to respond to an adequate trial of conservative therapy (generally considered to be two to four weeks

of bed rest). Chemonucleolysis at present has been approved for use only in adults and only in the lumbar area. It is not recommended as treatment for degenerative lumbar disc disease. Among the recognized contraindications are allergy to papaya derivatives, previous chemonucleolysis, previous lumbar disc surgery at the same interspace, rapid neurologic deterioration or the presence of other spinal pathology, such as spinal stenosis, spondylolisthesis and spinal cord tumors. Clinical findings and impressions should be confirmed by appropriate neurodiagnostic studies.

Chemonucleolysis is an operative procedure done in hospitals by surgeons who routinely manage lumbar disc problems, who possess training and current experience in disc surgery and who have received additional training in intradiscal therapy. The procedure is done either in the operating suite or the x-ray department under general or local anesthesia. Adequate x-ray facilities and anesthesia standby are essential. The patient is placed in a prone or lateral decubitus position and a long spinal needle is placed in the center of the nucleus pulposus under fluoroscopic control using a posterolateral approach. Discography is commonly carried out. Following a test dose, the definitive injection of chymopapain is made. The patient must be monitored carefully for several hours after the injection. Patients generally are discharged from hospital after several days of recuperation.

The results of chemonucleolysis are comparable to those of laminectomy and discectomy. Of properly selected patients, 70% obtain significant relief, though there is a 15% to 18% recurrence rate. It is of interest that of those patients who are not helped by chemonucleolysis, 90% are helped by subsequent laminectomy.

Anaphylactic reaction, a major deterrent to chemonucleolysis, occurs in about 1% of patients treated and results in a mortality rate of about 0.2%. Anaphylactic reaction seems to occur more frequently in women and in the presence of an elevated sedimentation rate. Preoperative treatment with corticosteroids and histamine blocking agents supplemented by adequate hydration has become commonplace. Other significant complications include chemical or bacterial discitis, mechanical injuries to the neural structures and inadvertent intrathecal injections.

In conclusion, chemonucleolysis is an operative procedure that is a viable alternative to lumbar laminectomy and discectomy for the treatment of documented herniated nucleus pulposus in carefully selected patients. It is not a panacea. Satisfactory results are directly related to proper patient selection. Some benefits of the procedure include minimal tissue disruption, shorter hospital stays, cost savings and better patient acceptance. With increasing clinical experience, there have been disappointing reports of poor results, prolonged severe back pain, prolonged hospital stay and a high incidence of recurrence necessitating further surgical treatment. A recent report by a manufacturer of chymopapain cites 21 cases of serious complications —paraplegia, cerebral hemorrhage and seizures—in 30,000 treated patients. It seems clear that the final chapters on chemonucleolysis remain to be written.

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Editorials

Footnote to the First Year

ONE YEAR AGO the Western Research Societies decided at their annual Carmel meetings to inaugurate the Clinical Investigation Section of *The Western Journal of Medicine*. Although the initial months were predictably slow, the flow of manuscripts in and out of my office the past six months has crescendoed nicely. In the first year we received and completely processed 30 manuscripts of which 50% were accepted. We published 14 articles (July and November 1983, February and March 1984). Most submissions were by researchers in California and Washington, the remainder coming from six other states. The manuscripts most frequently focused on areas in the subspecialties of infectious disease, endocrinology, cardiology and pulmonary disease. Thanks to a very energetic group of reviewers, the turnaround time for processing was quite short. On average, 31 days elapsed between the time the manuscripts were received in my office and the day I sent out the initial decision to the authors.

I conclude from all this that we are off to a fine start both quantitatively and qualitatively. If the crescendo persists, we will realize success in this venture by our second or third year. That will be sweet music, indeed. *The Western Journal of Medicine* will then be fully rounded out as a scientific medical journal and the Western Research Societies will feel justifiably proud of nurturing a valuable contribution to medical literature.

R. PAUL ROBERTSON, MD
Editor for Clinical Investigation

Hepatitis B Virus Infection and Primary Liver Cancer—An Unfolding Story

THE REVIEW in this issue by Vyas and Blum on hepatitis B virus infection illustrates how rapidly modern methods in molecular biology can be utilized to increase our understanding of pathophysiologic principles underlying human disease. Before 1979 the recombinant cloning of DNA from viruses known to be pathogenic in humans (including hepatitis B virus [HBV]) was prohibited in the United States and most other countries where such experiments could be done. When recombinant DNA guidelines were revised to permit these experiments, HBV DNA was cloned immediately in four different laboratories and the complete DNA sequence was determined within six months.[1-6] The cloned DNA was then used as a hybridization probe to detect integrated HBV DNA in a hepatocellular carcinoma cell line derived from a hepatitis B surface antigen (HBsAg) carrier, PLC/PRF/5,[7-10] and within one additional year integration of HBV DNA was reported in cases of primary liver cancer from many patients all over the world who were HBsAg carriers.[10-13] Integration of HBV DNA was also found in nontumorous liver of patients who had hepatocellular carcinoma[14,15] and in the liver genome of carriers who did not have hepatocellular carcinoma.[13-18]

From many epidemiologic studies, cited by Vyas and Blum, it was well established that persistence of hepatitis B virus infection—that is, the carrier state—is associated with increased risk of hepatocellular carcinoma developing and now it was also evident from molecular studies that HBV DNA had the capacity to integrate into the host genome and that such integration occurred before development of hepatocellular carcinoma. This strengthened the link between hepatitis B virus infection and primary liver cancer. It represented the first clear demonstration of a pathogenic DNA virus integrating into the human genome in a native host and established that HBV had properties consistent with those which might be expected for an oncogenic virus.

Like animal DNA tumor viruses—such as SV 40 and adenoviruses—in which integration of viral DNA correlates with the transformed state of cells in culture,[19] integrated HBV DNA shows rearrangement of both viral and adjacent cellular sequences at the site of integration.[20-22] A most exciting recent finding has been the observation by Rogler and Summers[23] of possible intermediates in the integration process. Using woodchucks, which are naturally infected with a virus, woodchuck hepatitis virus (which is structurally, molecularly and pathophysiologically related to HBV), these investigators cloned and characterized various molecular forms of woodchuck hepatitis virus from carrier woodchucks. Hepatocellular carcinoma develops in these animals rapidly and with extraordinarily high frequency during persistent woodchuck hepatitis virus infection.[24] In hepatitis virus carrier woodchucks in which liver cancer has not yet developed, Rogler and Summers have identified high-molecular-weight nonintegrated viral molecules with extensive sequence rearrangement,[23] as well as integrated viral molecules with simpler viral genome patterns and no rearrangement of flanking cellular sequences.[25] The correlation of these molecules with sequential events in the integration process and cellular transformation awaits further study. Cloning and characterization of integrated HBV DNA molecules from human primary liver cancer and a variety of cell lines derived from such tumors is also now in progress.[20-22]

Another potential use of molecular hybridization technology is in the clinical laboratory both as a diagnostic tool and in understanding the pathophysiology of chronic liver disease associated with persistent

hepatitis B virus infection. In carriers who are HBsAg-positive and hepatitis B e antigen (HBeAg)-positive, the situation is relatively clear. These patients have continued replication of virus in their liver, associated with chronic liver disease (chronic persistent or chronic active hepatitis), and are potentially infectious to their intimate contacts. However, in carriers who are HBsAg-positive and anti-HBe-positive (HBeAg-negative), who have generally been considered to be past the stage of active virus replication, liver disease has been thought to be quiescent (either absent or at an end stage with development of cirrhosis) and there is little or no potential infectivity. Recent studies with cloned HBV-DNA probes, however, have shown that a significant number of HBsAg- and anti-HBe-positive patients retain viral DNA in the serum.[26-28] They also have continued virus replication in liver and active chronic liver disease and may indeed be infectious.[29] Some patients with antibodies to HBsAg in their blood (anti-HBs), who were formerly thought to have recovered from hepatitis B virus infection, also retain virus in their liver and this is sometimes in integrated form.[30] It has also been found that some patients with hepatocellular carcinoma who are anti-HBs-positive have integrated HBV DNA in their tumors.[14,15,30]

These rather alarming findings—which may represent the exception rather than the rule—indicate the limitations of standard viral marker testing (HBsAg and HBeAg). This is especially relevant when both viral antigens and antibodies or immune complexes are present in the blood. Some of these patients can be identified using radioimmunoassays with monoclonal antibodies to HBsAg, developed by Wands and co-workers.[31] However, another category of patients who have chronic hepatitis show negative results with all traditional serologic HBV tests, yet analysis of serum or liver DNA extracts reveals the presence of molecules hybridizing with HBV-DNA probes.[30,32] These patients would have formerly been considered to have non-A, non-B hepatitis. Some show positive serologic reactions with monoclonal anti-HBs[32,33] and are, therefore, considered to be infected with HBV or a related virus. Others may represent cases of persistent hepatitis B virus infection that is truly latent—that is, no viral gene products are produced—whereas a third category may represent entities that have not yet been fully defined.[33]

From histologic, cellular and molecular studies it appears that persistent viral hepatitis type B generally falls into two categories, permissive infection and nonpermissive infection.[29,34-36] A mixed type of infection may also be found in which features of replicating and nonreplicating infection are present in different cells or regions of the same liver. The features of replicating or permissive infection include active inflammatory liver disease (chronic persistent or chronic active hepatitis), HBsAg and hepatitis B core antigen (HBcAg) production by individual hepatocytes distributed randomly throughout the liver parenchyma and free virions and lower molecular weight replicating forms of HBV DNA. The features of nonpermissive infection include no active inflammatory liver disease (the liver may show no histologic evidence of hepatitis B virus infection other than the presence of "ground glass" hepatocytes or inactive cirrhosis resulting from viral infection many years earlier); continued HBsAg but not HBcAg production, and integrated HBV-DNA molecules. In some of the latter cases, HBsAg production is present in groups or clusters of hepatocytes that have the nodular appearance of a focal clonal growth. In several of the latter cases, we have noted integration of HBV DNA into unique host sites, again suggesting monoclonality of these cells.[29] In those patients who are no longer actively replicating virus (nonpermissive infection), regardless of whether or not HBsAg continues to be produced, the presence of integrated HBV DNA in a unique banding pattern may have important implications in terms of risk for future development of hepatocellular carcinoma.

The studies reviewed here suggest that integration of the HBV genome represents an important event which occurs during the transformation of hepatocytes. Regardless of whatever role HBV eventually is shown to have in the pathogenesis of hepatocellular carcinoma, molecular biological techniques will have in great measure contributed to that knowledge. The use of these powerful new methods will permit studies on the replication of the hepatitis B virus and possible elucidation of how this virus alters hepatocyte function during persistent infection. It is hoped that this will bring us to a better understanding of cellular and molecular events that lead to the development of hepatic malignancy.

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A New Ball Game

MEDICAL PRACTICE has become a new and more complicated ball game—one that seems to be played with at least four balls. To win, one must keep all four in the air at once. The four balls are (1) modern medical science and technology, (2) the physician as a caring person, (3) the business aspects of medical practice and (4) the responsibilities of a professional in a changing society. Each of these four is brought into play in the care of any patient in these parlous times. A practicing physician will need to keep an eye on them all and juggle them appropriately in the care of patients, no matter what the practice arrangements may be. There is reason to believe that we are apt to be best at medical science and technology, that there has been some slippage in our behavior as caring persons, that we have much to learn about the economic and business aspects of patient care and that we are only just beginning to be aware of our responsibilities as the most significant health care professionals in a changing society. Each of these four requires our close attention in this new game in which we find ourselves. And of course we should play to win.

There is nothing fixed or static about any of this. Everything is changing and always in motion. We must be sensitive, resilient, adept masters of our art and science in the interests of our patients and the public. This will not be easy to do. We are not alone in the field of health care. Nor are we necessarily loved by everyone. There are others ready to assume our role. But individually and as a profession we are still held in considerable esteem. We are still very much in this new ball game and so each of its four "balls" is briefly discussed below:

Modern Medical Science and Technology

This has been the main focus of our attention for some decades. Many of us have become more concerned with the diseases people have than with the people who have these diseases and who, being human, are afraid, in pain or wanting to feel better. Our success in applying modern medical science and technology in patient care has greatly increased life expectancy at both ends of the life span and improved the technical care of disease and injury at any age. This has been a source of great personal and professional satisfaction. But too many of us have thought too little about the financial cost of this to patients and to society. We have worshipped at the altar of modern medical science and technology. We have strived to keep up with changes in this and on the whole have done quite well. We do not practice as we were taught in our formal training. We use new knowledge and new technology as these become available. It is essential that we keep current with this progress and its uses in patient care. (Ball #1.)

The Caring Physician

Our dedication—and success—in the practice of good scientific medicine has too often been at the expense of attention to the very personal human interaction between doctor and patient. This interaction is expected and needed by a patient who is fearful, is in pain and does not understand everything about

modern medical science and technology but wants to feel better. There is evidence that too many patients have not been satisfied and have been turning to other health professionals or to other health methods where they perceive that more attention is given to their human needs. And indeed many of them appear to be more satisfied and do feel better. Now that there will be more physicians in practice there should be more time for us to cultivate the very human doctor-patient relationship between one who is asking for help and one who agrees to try to help, that has always been the fundamental basis of all medical practice. Caring can also be a source of great personal and professional satisfaction for physicians. And done well it can surely make patients feel better and also strengthen the hand of our profession. (Ball #2.)

The Business of Medical Practice

The societal decision to foster economic competition in health care has greatly increased the importance of the business aspects of medical practice. The emphasis on this is new. Physicians generally have been regarded as poor at business. This will undoubtedly change. We are not stupid; if efficient business practices are now to be part of patient care we shall learn and apply them whether in individual or group practice, HMOs, IPAs, corporate medicine or whatever. The wise use of a dollar, whether in practice management or in patient care is now a necessary and accepted part of medical practice. It must become an integral part of every physician's practice. It is already a major collective concern of the profession. (Ball #3.)

A Professional in a Changing Society

American society is seeking a new accommodation with health care. Its cost is a matter of national concern. At issue is how much and what kind of health care can we afford. The public has not yet spoken on this subject although self-appointed spokesmen are heard loudly enough. In addition medical science and technology have begun to pose vexing ethical problems, particularly at either end of the life span. And the health care enterprise itself has become a very complex interdependent social, economic, political and technologic system. All of these issues are poorly understood. Physicians who see patients and the medical profession as a whole are very much part of it all. There is clearly a professional role to be played. Individual physicians and their medical associations are recognized as authoritative in matters of medical science and technology, and on what is wrong, what is likely to happen and what can be done about it in matters of health care. This professional role can be played in the care of patients and in the community, the state and the nation. It must be played and played well, if physicians are to remain in control of patient care, whether in a hospital or in society as a whole. (Ball #4.)

This new ball game is certain to be fascinating. It is already bringing new dimensions to medical practice and there will be still more. At the moment our task, individually and collectively as a profession, would seem to be to keep our eye on each of these four balls, and to try to keep them all in the air at once as we go about serving our patients and the public. MSMW

Overweight Is Risking Fate

ELSEWHERE in this issue is an article by Dr Eugene Boisaubin, "Approach to Obese Patients." Dr Boisaubin is to be commended for selecting the body-mass index (BMI) (weight [kg]/height [m]^2) as a way of expressing obesity. In the United States and in England, the use of this method for expressing deviations in body weight has been increasing steadily.[1,2] The BMI has several advantages over other indices. First, it has the best correlation with body fat measured in other ways of any measurement relating height and weight. Second, as a continuous variable, it increases steadily as body weight increases. Third, it provides a way of assessing both the degree of overweight and the risk associated with that excess weight.

The normal body-mass index is between 20 and 25 for men and women with a value of 25 (kg/m^2) corresponding to the upper limit for body weight in the life insurance and Fogarty Center tables.[1] A body-mass index between 25 and 30 is associated with excess weight and a low but measurable increase in risk to health.[2] A BMI of 30 is almost a 20% increase above the upper limits for normal weight. With a BMI above 30 a person is assuredly obese. Between a body-mass index of 30 and 40 the excess weight rises from 20% to 100% overweight and is associated with a moderate increase in risk to health. At a body-mass index of 40 the excess mortality in the life insurance data is more than 250% above that for persons of normal weight.[3] Thus, with a BMI of 40 or above a person is morbidly obese with a high degree of risk to health.

Another advantage of the BMI is that it can be used as a guide to treatment. When the BMI is below 25, the only appropriate ways of losing weight, if this is to be done for cosmetic reasons, is to use diet and exercise. When the body-mass index is between 25 and 30, and particularly when it is close to 30, it is often desirable to encourage efforts at weight loss, including behavioral change, exercise and conventional and low-calorie diets. When the body-mass index is between 30 and 40 a more intensive approach to weight control is desirable, including, under the appropriate circumstances, pharmacologic agents. When the risk of obesity is high with a body-mass index of more than 40, even such a drastic approach as a surgical procedure may be considered. As Dr Boisaubin points out in discussing the physician's role in the treatment of obesity, "empathy is so important in approaching fat patients that

physicians who have negative feelings [toward obesity] should immediately refer the patients to another physician who has greater interest."

It has recently been suggested from an analysis of the various studies relating weight to health that it may not be hazardous to be overweight as one grows older; it may indeed be healthier.[4] In a careful analysis of this proposition, a recent Working Party Report from Great Britain pointed out that this interpretation results from lumping smokers and nonsmokers.[2] When these are separated, as was done in a recent study from the American Cancer Society,[5] there is no protective effect of being overweight. Indeed, even the Framingham study has now recognized obesity as an independent risk factor for cardiovascular disease.[6] The percentage of desirable weight at the initial examination predicted the 26-year incidence of coronary disease in both men and women.[6] "It can be estimated from the Framingham data that if everyone were at optimal weight we would have 25% less coronary heart disease and 35% less congestive failure and brain infarctions."[7]

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Case Reports

Von Willebrand's Disease and Severe Gastrointestinal Bleeding

Report of a Kindred

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VON WILLEBRAND'S DISEASE has been reported in association with hereditary hemorrhagic telangiectasia,[1,2] gastrointestinal angiodysplasia and persistent gastrointestinal hemorrhage.[3,4] In addition, angiodysplasia and acquired von Willebrand's disease have been associated.[5,6]

We describe a kindred in which multiple members are afflicted by both von Willebrand's disease and severe, recurrent, multifocal gastrointestinal hemorrhage.

Report of a Case

A 42-year-old woman, the mother of five children, was referred for evaluation and management of chronic gastrointestinal tract hemorrhage manifested by recurrent melena. The bleeding occurred over a period of two years, was intermittent, made numerous blood transfusions necessary and was not associated with other spontaneous hemorrhages or cutaneous telangiectasias. The source remained unknown after an evaluation that included three upper gastrointestinal panendoscopies, two indium-tagged erythrocyte scans, barium meal and barium enema and arteriography of the superior mesenteric, inferior mesenteric, bilateral renal and celiac distributions—all done during periods of active bleeding. She had been treated with biweekly transfusions of cryoprecipitate, intravenous administration of vasopressin and cimetidine by mouth without reduction in transfusion requirements.

The medical history was significant for von Willebrand's disease in the patient (Figure 1, III 8) and in 18 of 45 maternal relatives, segregating in the classic autosomal dominant manner. The patient's Ivy bleeding time was more than 30 minutes (normal less than 7 minutes), the partial thromboplastin time was 68 seconds (normal 40±3 seconds) and the prothrombin time was 14 seconds (normal 14±2 seconds). Antihemophilic factor activity was 44% (normal 50% to 150%). The prolonged partial thromboplastin time in association with a relatively minor reduction in the antihemophilic factor activity has not been fully explained. Three affected daughters (IV 6, 7 and 8) and one maternal uncle (II 5) whose values were available had prolonged bleeding times and low factor VIII activity levels. Twenty family members were screened with factor VIII assays in 1976 and values were in the range of 25% to 45%. A cousin (III 18) had abnormal ristocetin-induced platelet aggregation, a bleeding time of more than 20 minutes, factor VIII activity of 25%, a prolonged partial thromboplastin time and a normal prothrombin time. The partial thromboplastin time returned to normal after transfusion of cryoprecipitate.

Of the 19 members in this kindred with von Willebrand's disease, 6 were also afflicted with severe recurrent gastrointestinal bleeding with onset usually in middle life and of a similar clinical nature. In no case did severe gastrointestinal bleeding occur in a family member with a normal factor VIII level. A niece (IV 19) had suffered a hemarthrosis from mild injury and mild occult gastrointestinal bleeding by age 26. An uncle (II 5) died of gastrointestinal hemorrhage, found at autopsy to be from diffuse jejunal and colonic mucosal bleeding, and three other relatives died of uncontrolled bleeding after relatively minor trauma or surgical procedure. A cousin (III 18) has a history of particularly severe multiple massive bleeding episodes from unidentifiable gastrointestinal sources. He has undergone exploratory laparotomy at least four times with resection of portions of stomach, intestine and colon without sustained benefit. Severity of bleeding was not related to the factor VIII activity level. After transfusion with cryoprecipitate, the bleeding time and factor VIII level returned to normal and there was no trouble with hemostasis at operation, but gastrointestinal bleeding persisted. At last count he had received more than 4,000 units of blood and had been for many years in a Veterans Administration hospital.

Discussion

Classic von Willebrand's disease is an autosomal dominant coagulopathy manifested clinically by epistaxis, impaired hemostasis with surgical procedures, injury or parturition and mild mucosal bleeding in heterozygous persons and, rarely, by more severe features such as hemarthrosis in homozygous persons. There may be considerable variability in both clinical and laboratory manifestations between families, between persons within a family and in persons at different times. An acquired form of the disease is recognized[7] and has also been associated with angiodysplasia.[5,6]

Results of laboratory tests in cases of von Willebrand's disease are characterized by decreased factor VIII activity, a prolonged partial thromboplastin time

(Bush RW, Huff JW: Von Willebrand's disease and severe gastrointestinal bleeding—Report of a kindred. West J Med 1984 May; 140:781-783)

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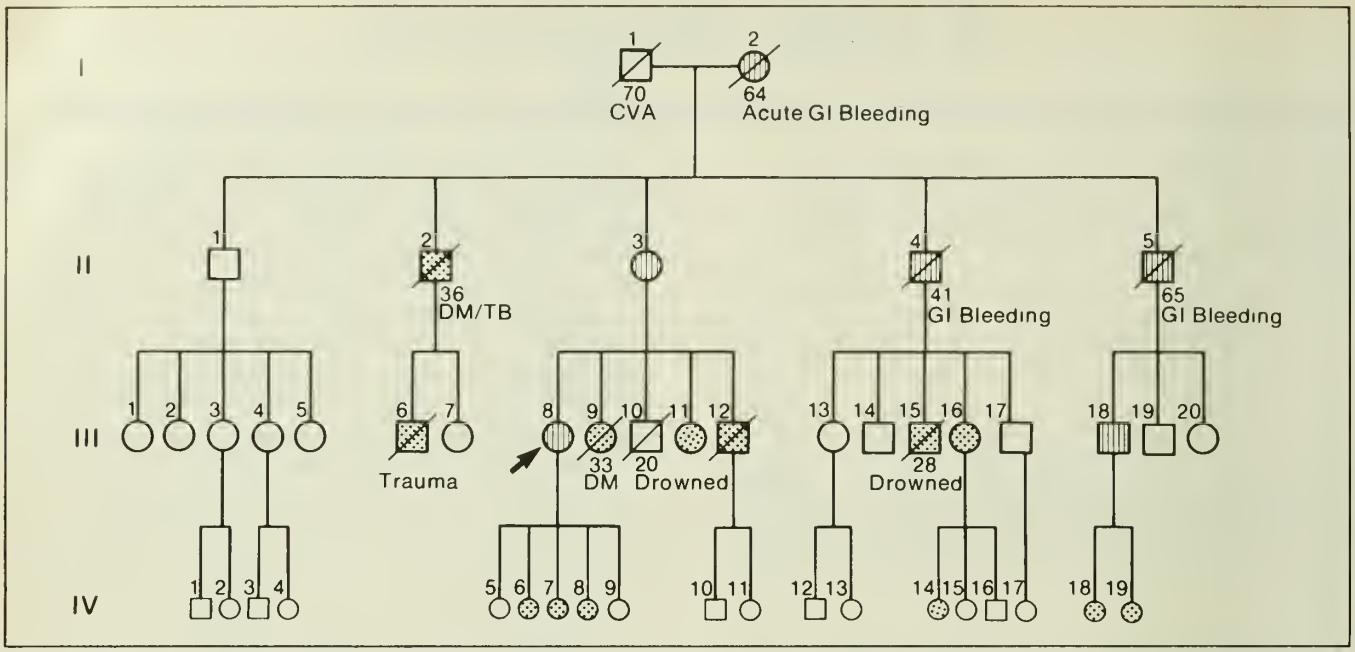

Figure 1.—The pedigree chart of a 42-year-old woman who has von Willebrand's disease with severe gastrointestinal (GI) bleeding. ○ = normal female, □ = normal male, ○ = von Willebrand's disease, ○ = von Willebrand's disease with severe GI hemorrhage, ⊘ = deceased, cause of and age at death if known, ↗ = propositus. Abbreviations: CVA = cerebrovascular accident, DM/TB = diabetes mellitus and tuberculosis.

ABBREVIATIONS USED IN TEXT

VIII-RAg = factor VIII-related antigen
vWF = von Willebrand factor

and by impaired ristocetin-induced platelet aggregation with a prolonged bleeding time.

Normal factor VIII is a molecular complex of a lower-molecular-weight procoagulant molecule, encoded by an X-linked gene, bonded noncovalently to a high-molecular-weight (230,000) polymeric glycoprotein that contains factor VIII-related antigen (VIII-RAg) and von Willebrand factor (vWF). VIII-RAg in plasma is synthesized by vascular endothelium as a low-molecular-weight molecule that polymerizes and is secreted into the plasma.[8,9] Current explanations suggest that the low-molecular-weight form exhibits VIII-RAg determinants and the larger polymers constitute vWF activity or platelet adhesion mediator (Figure 2).[10,11]

This kindred shows a syndrome of an unusually severe hemorrhagic disorder that includes hemarthrosis, epistaxis requiring blood transfusion and protracted hemorrhage with parturition and dental extraction, as well as severe, recurrent, multifocal bleeding from the gastrointestinal tract, probably from acquired angiodysplastic lesions. It might be postulated that the endothelial cells lack not only the biosynthetic ability to produce the active VIII-RAg/vWF complex, but also the anatomic integrity necessary to maintain a competent vascular conduit. Booyse and co-workers have shown similar coexisting defects in cultured endothelial cells of humans with von Willebrand's disease.[12]

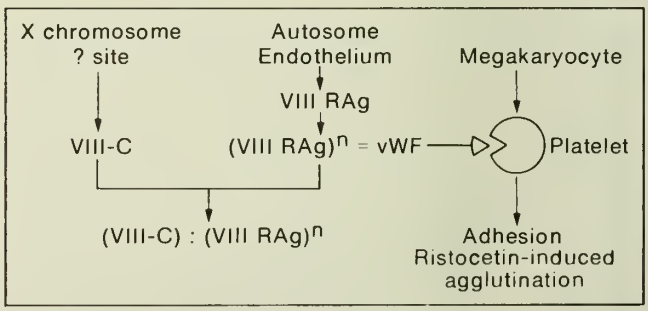

Figure 2.—Schematic representation of a theory of von Willebrand factor (vWF) source and function. VIII-C = factor VIII procoagulant antihemophilic factor, VIII-RAg = factor VIII-related antigen, $(\text{VIII-RAg})^n$ = polymer = von Willebrand factor.

One smaller kindred with similar manifestations has been described,[2] as well as two unrelated cases,[3,4] but none have been of the severity or strong familial concordance as that presented here. As suggested by Conlon and associates,[2] it is difficult to associate endothelial cell deficits in both biosynthetic ability and anatomic integrity in these patients by chance alone.

These patients present a difficult management problem with multifocal, widespread lesions rendering surgical correction futile, yet requiring overwhelming blood product support for the maintenance of erythrocyte mass. In addition, they may indicate the anatomic site of the pathophysiologic lesion of von Willebrand's disease.

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Non-01 *Vibrio cholerae* Gastroenteritis in Northern California

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CHOLERA is usually regarded as an exotic disease of the Asian and Middle Eastern countries that is rarely seen in the United States. Most of the cases reported in the United States have been caused by non-01 *Vibrio cholerae* organisms and have followed either raw seafood ingestion or foreign travel. We report an isolated case from northern California of a patient who acquired a non-01 *V cholerae* infection and a classic cholera-like syndrome but who had not eaten raw seafood or traveled out of the country. Reports of cases of non-01 *V cholerae* gastroenteritis occurring in California have been exceedingly rare.

Report of a Case

A previously healthy 18-year-old man, a surfer, was seen in our emergency room because of nausea, vomiting, diarrhea and abdominal cramps for ten days; 24 hours before, the diarrhea had increased dramatically and the patient had progressive weakness, malaise and decreased urinary output. On physical examination he was severely dehydrated and had dry, puckered mucous membranes, sunken eyeballs, loss of skin turgor and peripheral cyanosis. He was afebrile, his blood pressure while supine was 110/60 mm of mercury accompanied by substantial postural hypotension, pulse rate was 150 per minute and respirations 28. The abdomen was mildly tender with active bowel sounds; rectal examination showed no abnormalities.

Admission laboratory studies disclosed the following values: hematocrit 63%, hemoglobin 20.8 grams per dl, leukocyte count 39,900 per μl; serum glucose 325, blood urea nitrogen 52 and creatinine 5.1 mg per dl; arterial pH 7.13; bicarbonate 7.6, sodium 137, chloride 99 and potassium 4.5 mEq per liter; serum was negative for ketones. Analysis of urine showed proteinuria (3+), 20 to 30 leukocytes per high power field, 10 to 20 erythrocytes per high power field and a specific gravity of 1.005. Urine sodium level was less than 10 mEq per liter, urine potassium 60 mEq per liter and urine osmolality 443 mosm per liter. Blood specimens were sent for culture, results of which continued to be negative.

The patient's condition was diagnosed as severe dehydration with anion-gap metabolic acidosis and prerenal azotemia due to the loss of fluids by diarrhea, and a diarrhea workup was initiated. Stool specimens on naked eye examination were light green and watery without blood or mucus and microscopic examination showed no leukocytes, erythrocytes, ova or parasites. On sigmoidoscopic examination there was mild congestion of the mucosa. Stool specimens were negative for routine pathogens but grew out a vibrio moderately heavy in amount on special medium (thiosulfate-citrate bile salts) and was subsequently classified as non-01 type. These specimens were also sent to the state laboratory and the Centers for Disease Control to confirm the growth of non-01 *V cholerae*.

Treatment was begun by replacing fluids intravenously via a central venous pressure line placement. Intravenous fluid replacement was started with 5% dextrose in water and half normal saline, sodium bicarbonate and potassium chloride and augmented to match his high outputs: 24-hour infusion volumes over the first three days totaled 7,765, 9,800 and 10,800 ml, respectively. Outputs concomitantly were 5,900, 7,740 and 7,800 ml over this same period, mostly in the form of massive diarrhea. A regimen of doxycycline hyclate, 100 mg given by mouth every 12 hours, was started on the third hospital day when the stool cultures grew *Vibrio*. His recovery was uneventful and he was discharged on the tenth hospital day with complete return of renal function and cessation of diarrhea after a seven-day course of doxycycline. Further stool cultures for vibrios remained negative.

On repeated questioning he said he had not traveled outside his immediate area of residence or ingested any raw or poorly cooked seafood. On questioning family members, there was no history of diarrheal illness elicited. The County Health Services Agency took water samples from the home of the patient (negative) and

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from the beach waters where he regularly surfed, which was near an area of sewage effluent. Non-01 *Vibrio cholerae* was isolated not only from the sea water but eventually from two nearby freshwater creeks as well, about 5 and 25 miles from the site of original contamination.

Discussion

De Gerome and Smith[1] reported the first case of non-01 vibrio infection contracted in this country in a patient who had visited New Orleans and in whom a prolonged diarrheal illness developed. Hughes and associates[2] described 26 patients seen between January 1972 and March 1975 and felt there had been a dramatic increase in the number of non-01 *V cholerae* isolates referred to the Center for Disease Control for identification. Thirteen (50%) organisms were isolated from stool specimens of patients having acute diarrheal illness and most of the patients had a history of recent shellfish or raw seafood ingestion or foreign travel. In 1981 Morris and co-workers reported 14 more sporadic cases of non-01 *V cholerae* gastroenteritis who had diarrhea, abdominal cramps and fever; the patients with domestically acquired cases had a recent history of eating raw oysters, whereas the other patients had traveled outside the United States.[3] Non-01 *V cholerae* gastroenteritis is increasingly being recognized as a clinical entity and can produce an acute diarrheal illness identical to classic *V cholerae or Vibrio parahaemolyticus* gastroenteritis. *V parahaemolyticus* gastroenteritis also begins abruptly with explosive watery diarrhea and abdominal cramps but subsides spontaneously within 24 to 48 hours. *V parahaemolyticus* does not produce a cholera-like enterotoxin whereas non-01 *V cholerae* can produce a toxin virtually identical to the cholera enterotoxin.[4]

Most of the domestically acquired cases have been contracted in the Texas-Louisiana gulf coast region after raw seafood ingestion.[3] The actual incidence of non-01 *V cholerae* gastroenteritis may be even greater than previously recognized because only patients with severe diarrhea and dehydration seek medical help.[5] Systemic non-01 *V cholerae* infections have been described in immunocompromised and debilitated patients after occupational or recreational exposure to salt water without classic gastroenteritis.[2] Surprisingly, the reported incidence of vibrio infections in California is low despite the significant numbers of people traveling in and out of this state from other countries. Our one case represents an unusual exposure to the pathogenic organism related to offshore surfing near an area of sewage effluent. In none of the other surfers using this area did any symptoms whatsoever develop and we have not seen any additional cases of similar infection in our county to date.

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Carotid Artery Bruits and Lacunar Strokes

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SEVERAL RECENT SURVEYS have shown a surprisingly high frequency of carotid artery bruits among asymptomatic adults: 2.1% to 3.1% at ages 45 to 54; 4.0% to 4.2%, ages 55 to 64, and 7.0% to 7.1%, ages 65 to 74.[1,2] These bruits may serve more as nonspecific markers for generalized vascular disease than as harbingers of stroke in an area distal to the involved carotid artery.[1-3] Lacunar infarcts appear to be decreasing in frequency, but they are still common, with an autopsy prevalence of 8%.[4] Fisher showed a significant association of atherosclerosis and lacunar disease in a large unselected autopsy series.[5] There appeared to be no correlation between presence or severity of internal carotid atherosclerosis and lacunar disease. However, there is scant mention in the literature of a carotid bruit in association with a lacunar infarct. Herein are reports of cases of two patients with carotid artery bruits who had typical lacunar stroke syndromes ipsilateral to severe internal carotid artery disease.*

Reports of Cases

CASE 1. The patient, a 69-year-old right-handed man, had been known to have moderately severe hypertension for at least 15 years. He had been admitted to hospital in 1971 and 1973 for two episodes of congestive cardiac failure attributed to hypertension. In the late 1970s renal insufficiency developed and he had a serum creatinine level of 2.5 to 3.5 mg per dl. His antihypertensive regimen at the time of his stroke included 40 mg a day of furosemide, 10 mg a day of metolazone, 0.4 mg twice a day of clonidine hydrochloride (β-blockers had caused bronchospasm) and 5 mg twice a day of minoxidil. On this regimen his blood pressure measurements ranged from 130 to 160 mm of mercury systolic and 90 to 100 mm of mercury diastolic.

In addition to hypertension he had a five-year history of type II diabetes mellitus, treated with insulin, and

*Bernard Bodmer, MD, and David Giles, MD, provided technical help in analyzing these cases.

(Hindson DA: Carotid artery bruits and lacunar strokes. West J Med 1984 May; 140:784-786)

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hypercholesterolemia—his serum cholesterol values ranging from 290 to 330 mg per dl with normal triglycerides. There was an insignificant, remote cigarette-smoking history.

Severe diffuse peripheral vascular disease was present. In 1979 aortography, done because of claudication of both hips and legs, showed severe atherosclerotic disease of the distal aorta and both iliac arteries. In February 1981 he had lower abdominal and back pain and underwent emergency excision of a 5-cm abdominal aortic aneurysm for "impending dissection," from which he recovered without event. In June 1982 sudden weakness and loss of coordination of his right leg developed. He did not seek medical attention, and the weakness resolved over ten days to two weeks. In September 1982 a left carotid bruit was detected. Ultrasonic imaging showed moderate atherosclerosis of both carotid bulbs without identifiable ulceration. Color-coded Doppler imaging showed about 50% to 70% stenosis of the right internal carotid artery and 80% stenosis of the left internal carotid artery at the bifurcation. He refused to consider arteriography and surgical treatment. He had no other neurologic events or amaurosis fugax until January 1983.

In January 1983 he had sudden onset of numbness and clumsiness of his right side. There were no other symptoms. On physical examination the patient was plethoric and had a blood pressure of 180/90 mm of mercury. Cardiorespiratory examination showed no abnormalities except for an S_4 gallop. There were systolic bruits heard over both femoral arteries and no popliteal or pedal pulse could be palpated. There was a systolic bruit over the left carotid artery at the angle of the jaw, but carotid pulses, as well as preauricular and temporal pulses, were full and equal. There was a right hemisensory deficit to all basic modalities with near-perfect midline splitting. His gait was unsteady and he was unable to tandem walk. He could walk on his heels or toes, however, and detailed testing showed no abnormality in muscle strength or tone. Rapid rhythmic alternating movements, finger-to-nose, heel-to-shin and foot-tapping tests were done normally and symmetrically.

There was rapid resolution of the gait disorder and the patient was walking normally by a week. There was slower resolution of the sensory deficit and by four weeks after the ictus there was a barely detectable decrease in sensation to pin and light touch on the right side. A computed tomographic (CT) scan done 14 days after the event showed no abnormalities.

Case 2.* The patient, a 64-year-old right-handed man, had had known hypertension for at least six years and was being treated with chlorthalidone and clonidine; blood pressure readings ranged from 150 to 180 mm of mercury systolic and 90 to 100 mm of mercury diastolic. He had a 50-pack-year history of smoking. There was no diabetes mellitus or hyperlipidemia. In 1977 a right aortofemoral bypass graft had been done for intermittent claudication. In September 1982 he underwent left iliac artery angioplasty for hip and calf claudication. At that time a left carotid bruit was heard. Ultrasonic imaging showed extensive atherosclerotic disease in the right internal and external carotid arteries, less severe disease in the left internal and external carotid arteries and no ulcerations. He had no history suggestive of transient ischemic attacks, stroke or amaurosis fugax until February 1983.

In February 1983 the patient awakened with weakness on the left side of his body and slurred speech. On physical examination there were bilateral carotid bruits, louder on the right, with normal pulses. Initial neurologic examination showed a left hemiparesis with left central facial weakness, deviation of the uvula to the right, slurred speech, profound weakness of the left arm and leg and a plantar extensor response on the left. He was fully oriented, responded appropriately and was aware of his deficit. He was able to draw a clock face accurately with all numbers, hour and minute hands for several different requested times. Sensation was intact to all basic modalities without extinction. He was able to identify numbers written on either palm and could distinguish among various coins placed in either hand (with help closing left hand and moving coin about). Later in his hospital course there was suggestion of extinction of response to left-sided visual threat and of some left hemineglect. He showed substantial improvement in his weakness after one to two days and by seven to ten days there was only minimal weakness of the upper extremity and he could walk with a cane. He was able to dress, feed and shave himself.

Color-coded Doppler carotid imaging showed an apparent total occlusion of the right internal carotid artery, 50% stenosis of the left internal carotid artery and 70% or greater stenosis of the right and left external carotid arteries. A CT scan done six days after the stroke showed a 1-cm ill-defined lucency in the right basal ganglia (Figure 1).

Discussion

The first case represents a typical example of a pure sensory stroke, which has been excellently reviewed recently.[4,6,7] The remarkable midline split and involvement of face, arm and leg seen in this case are felt to be indicative of ischemia in the thalamus and not the superficial cortical areas or brain stem. CT studies have been unrevealing in nearly all instances. In the few cases studied at autopsy the lesion has been in the ventral posterior nucleus of the thalamus. This area is supplied by the small (100 microns) thalamoperforants arising from the posterior half of the circle of Willis and the stems of the posterior cerebral arteries. The presumed arterial pathology is lipohyalinosis, microatheroma of the penetrating arteries or atherosclerosis of the posterior cerebral artery with involvement of the origin of the penetrator. While microembolization is inferred to be the cause in some cases of lacunar stroke,[8] this is not a likely mechanism for the smaller infarcts causing a pure sensory stroke. Fisher comments in his review of 135 cases of hemisensory symptoms,

*Phillip Levy, MD, gave permission to include this case.

Figure 1.—A computed tomographic scan showing a 1-cm ill-defined lucency in the right basal ganglia.

including 58 patients with pure sensory stroke, that none had carotid disease "by clinical and laboratory assessment short of routine angiography."[7] Angiography was not felt to be indicated clinically but would have helped delineate the extent of carotid artery disease and the relative contribution of the internal carotid and basilar arteries to the posterior cerebral artery. While this patient had a carotid bruit and ultrasonic-Doppler evidence of internal carotid disease on the appropriate side, the infarct was most likely in the thalamus and unrelated to the carotid disease.

The second case is a typical example of pure motor hemiplegia. This syndrome is defined by weakness or paralysis of the face, arm and leg on one side without sensory deficit, hemianopia, aphasia, apraxia or agnosia in the acute phase. Pure motor hemiplegia is caused most often by a capsular infarct, occasionally by a pontine infarct and rarely by a variety of other causes in other areas of the central nervous system.[6] Rascol and co-workers reported on 30 cases of pure motor hemiplegia. No carotid bruits were described, and angiography done in 21 patients did not show carotid artery disease. In 29 of the 30 patients, a lesion able to explain the stroke was found by CT study. They describe three varieties of ischemic capsular lesions: type I, capsulo-putamen-caudate; type II, capsulo-pallidal, and type III, anterior capsulo-caudate. The lesion seen on CT study in case 1 is in the posterior limb of the internal capsule and corona radiata and corresponds best with a type I infarct. This area is supplied by the lateral lenticulostriate branches of the middle cerebral artery. Embolization to this area from internal carotid artery disease is certainly possible, but this seems unlikely in this patient who has apparent occlusion of the internal carotid.

Aleksic and George reported on two cases of pure motor hemiplegia with occlusion of the extracranial internal carotid artery.[10] They assumed a causal relationship in their cases and postulated that a reduction in mean pressures distal to carotid artery stenosis or occlusion might cause thrombosis to occur in the small penetrating arteries supplying the internal capsule. There is no way of proving or disproving this hypothesis, but such a mechanism seems no more likely than fortuitous association. Indeed, Fisher has suggested that internal carotid stenosis might be protective against ipsilateral lacunar strokes by lowering intracranial arterial pressure.[5]

Patients who have an asymptomatic carotid bruit or even documented internal carotid artery stenosis may not be at significantly greater risk for stroke in the territory of that carotid artery than matched controls.[1,2,11] This conclusion is controversial but, if correct, would mitigate against consideration of surgical therapy in an asymptomatic patient. One of the many areas of debate is what symptoms are related to internal carotid disease.[3] The cases reported here represent yet another problem in interpreting symptoms. The lacunar syndromes of pure sensory stroke or pure motor hemiplegia are unlikely to be related to internal carotid artery disease. However, a characteristic of many lacunar strokes—and a feature seen in the cases reported here—is significant improvement in the neurologic deficit over days to weeks. If such patients are not evaluated until some time after the event, then the ability to distinguish a lacunar stroke from cortical ischemia might be quite difficult and the temptation for surgical intervention increased. Awareness of the clinical features of the various lacunar strokes, early detailed neurologic evaluation and later CT scanning should allow distinction between lacunar strokes and symptoms related to internal carotid artery disease.

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Death From Cysticercosis

Seven Patients With Unrecognized Obstructive Hydrocephalus

JAMES R. KEANE, MD, *Los Angeles*

CYSTICERCOSIS, THE INFESTATION of larval pork tapeworms in humans, primarily involves the central nervous system. Common clinical presentations include seizures, subacute meningitis, intracranial masses and obstructive hydrocephalus.[1,2]

Largely eliminated in the United States by the turn of the century through improved sanitation and careful meat inspection, cysticercosis remains an endemic disease in much of the world. Increased immigration from the pandemic regions of Mexico and Central and South America has made cysticercosis currently a common disease in the southwestern United States.[1,2]

Deaths from cysticercosis are particularly tragic because the active disease affects predominantly young adults. Obstructive hydrocephalus, the principal cause of death, is treatable if diagnosed in time. The following cases illustrate the problems in recognizing the obstructive manifestations of cysticercosis, even in an area where cysticercosis is a common and anticipated cause of neurologic complaints.

Reports of Cases

CASE 1. A 29-year-old Ecuadorian woman was admitted to another hospital with severe headaches in 1965. Evaluation included angiography and pneumoencephalography, and results were normal aside from cerebrospinal fluid showing increased pressure with minimal pleocytosis of five mononuclear cells per μl.

She was discharged with a diagnosis of benign intracranial hypertension and did well for five years, when headache and blurred vision returned, accompanied by transient numbness of the left side of her face and her left arm. Inpatient evaluation elicited only a mild meningeal reaction thought to represent recurrent cysticercal meningitis.

She was lost to follow-up until she arrived at the emergency room three months later, in stupor, with extensor posturing "seizures." She had respiratory and then cardiac arrest and resuscitation was of no avail.

Autopsy showed hydrocephalus due to obstruction of the right foramen of Monro by a cysticercal cyst.

CASE 2. For six months a 25-year-old Mexican-born woman had headache, nausea and vomiting. For three months she had occasional brief lapses in consciousness preceded by severe crescendo headaches. She consulted several physicians without a definite diagnosis being made.

Three days before admission, her headaches became very severe, but no specific diagnosis was made on visits to still another physician and to a local emergency room. She then experienced an excruciating headache, was seen to shake bilaterally, stopped breathing and fell to the floor.

On arrival at the hospital, she was apneic and had fixed pupils. Ventriculostomy in the emergency room showed fluid under very high pressure (50 mm of mercury). A subsequent computed tomographic (CT) scan with ventricular instillation of metrizamide showed a mobile cyst within a dilated left lateral ventricle. Brain-stem activity did not return and she was pronounced dead later on the day of admission.

Autopsy confirmed the diagnosis of cysticercosis.

CASE 3. A 10-year-old girl from El Salvador had been in the United States two months when headaches, nausea and vomiting developed. Three days later, because of persisting symptoms now accompanied by lethargy, she was admitted to another hospital. Admission examination showed a lethargic, afebrile girl with normal optic discs, equal pupils and mild neck stiffness. A lumbar puncture done to rule out meningitis showed 18 leukocytes, normal protein and glucose values and a pressure of 210 mm of cerebrospinal fluid.

The following day, before a scheduled CT scan could be done, the patient stopped breathing. Tracheal intubation and assisted respiration were instituted but she remained in coma with fixed pupils. She was transferred to Los Angeles County-University of Southern California (LAC-USC) Medical Center where a CT scan showed hydrocephalus with moderate dilatation of the left lateral ventricle. A ventriculostomy was done but her condition failed to improve and she died on the third hospital day.

Autopsy showed a 2-cm cysticercal cyst in the left lateral ventricle occluding the foramen of Monro (Figure 1).

CASE 4. Headaches developed in a 16-year-old Mexican-born woman 15 months before she died. They were treated with analgesics by her family doctor. Three months later intermittent numbness of the right side of her face and right arm began to accompany her headaches, and a history of apparently similar headaches and numbness in a cousin was obtained. A diagnosis of migraine was proposed, and ergotamine treatment appeared to be of benefit.

She returned to Mexico and was lost to follow-up until the day of admission when she awoke with a severe headache accompanied by nausea, vomiting, blurred vision and extremity and tongue numbness. She was taken to a local emergency room but, while being examined 4½ hours later, she suddenly became unresponsive and stopped breathing.

On transfer to our hospital three hours later, she was comatose without spontaneous respirations; her optic discs were normal; the pupils were equal and reactive,

(Keane JR: Death from cysticercosis—Seven patients with unrecognized obstructive hydrocephalus. West J Med 1984 May; 140:787-789)

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Figure 1.—(Case 3) Horizontal brain section showing cysticercal cyst in the left lateral ventricle. (Photograph courtesy of Dr Carol Miller, Department of Pathology, Los Angeles County-University of Southern California Medical Center.)

and her eyes were held in upward gaze, though full horizonal eye movement could be elicited by head rocking. A CT scan showed hydrocephalus and immediately a ventriculostomy was done.

She died on the fifth hospital day without regaining consciousness. An autopsy confirmed the diagnosis of cysticercosis with obstruction of the cerebral aqueduct.

Case 5. A 19-year-old Mexican-born woman was seen in an emergency room complaining of headache, nausea and vomiting of three months' duration. A tentative diagnosis of migraine was made, and she was scheduled for a CT scan.

On return to the emergency room ten days later, she was admitted to hospital with a diagnosis of severe migraine headache. Eight hours after arrival, she had a respiratory and then a cardiac arrest and could not be resuscitated.

Autopsy showed obstructive hydrocephalus due to cysticercosis.

Case 6. A 27-year-old Mexican-born woman was en route to hospital with a severe headache when she stiffened and became unresponsive.

Her headaches, which had begun three months earlier, increased in severity the week before admission and were joined by nausea and vomiting. The day before admission, she had been seen at another emergency room and sent home with analgesics.

On arrival at the LAC-USC Medical Center, she was comatose with fixed pupils. Following a decompressive ventriculostomy, she became slightly more responsive and pupillary reactions returned. A CT scan showed generalized ventricular dilatation. She died on the fifth hospital day without regaining consciousness.

Autopsy showed a large cysticercal cyst in the fourth ventricle with secondary hydrocephalus.

Case 7. A 32-year-old Mexican-born woman had suffered from intermittent severe headaches for 14 years. Three months before death, a more severe headache developed, accompanied by vomiting, dimming of vision and fleeting diplopia. Ophthalmologic and neurologic examinations showed no abnormalities and a tentative diagnosis of migraine headaches was made.

Her headaches persisted and intermittent transient numbness of the right side of her body developed. A repeat neurologic examination a month later again showed no abnormalities.

On the day of admission, she experienced a crescendo headache, vomited and lost consciousness. On arrival at our hospital she was apneic without palpable pulses. A CT scan showed dilatation of the right lateral ventricle with secondary transtentorial herniation. She failed to regain any brain-stem activity and died the next day.

Autopsy showed several cysticercal cysts in the third ventricle as the cause of the right foramen of Monro obstruction.

Discussion

These patients had symptoms of nonlocalized increased intracranial pressure: headaches, nausea and vomiting. In the absence of secondary signs of increased pressure, such as papilledema or abducens nerve palsy, there was little distinctive early in their course in either history or physical examination to indicate the seriousness of their condition. Commonly, a diagnosis of vascular headache was made and the patients were treated with analgesics.

Most of our patients had headaches with vomiting for many months and repeatedly sought medical attention. Later, development of fleeting diplopia (one patient), transient unilateral numbness (three patients) and crescendo headache with syncope (one patient) appropriately caused concern, but physicians were falsely reassured by the absence of abnormalities on examination.

These associated symptoms are more valuable in suggesting the presence of an intracranial mass than are any specific characteristics of the head pain itself. Postural precipitation of headache, though "classical" for an intermittent cerebrospinal fluid obstruction by a third-ventricle colloid cyst, is actually uncommon in that condition[3] and was not reported by our patients. Paroxysmal headaches, identical to those of our patients, *are* common with colloid cysts, but this quality leads to the same misdiagnosis of migraine in that con-

dition.[4] Tumor headaches typically worsen with sudden head movements and with coughing and straining, but so do many benign vascular headaches. Tumor headaches characteristically are worse in the morning, but many more morning headaches are due to depression than to brain tumors. Long-standing headaches are likely to be benign. However, patients with life-threatening cysticercosis may experience chronic headaches either from a protracted course of intermittent hydrocephalus or from repeated exacerbations of cysticercal inflammatory activity.

During the terminal episode of hydrocephalus, four patients managed to reach a hospital from 4 to 24 hours before irreversible midbrain damage occurred. Prompt CT scanning and decompressive ventriculostomy would have saved their lives.

Papilledema was specifically sought in all patients, and its absence was falsely reassuring. During the period in which these seven patients died, at least 64 other cases of hydrocephalus due to cysticercosis were diagnosed at our hospital. In most of these successfully treated cases, recognition of early papilledema was the principal spur to prompt diagnosis.

In patients such as ours who have intermittent cerebrospinal fluid obstruction, the presence or absence of a retinal vein pulsation is of limited diagnostic value. The retinal venous pulse often is absent in normal persons.[5] The presence of such a pulse, with rare exceptions, indicates that the intracranial pressure is normal at that moment. A venous pulse occasionally coexists with an intracranial mass, however, and rarely is present despite mild papilledema—presumably during periods of normal intracranial pressure.

The CT scan has diminished the role of lumbar puncture and somewhat muted the debate about its risks. Pre-CT experience at our hospital, when a great many spinal taps were done on patients with unsuspected intracranial masses, suggested that such risks are minimal. Whatever the exact danger, spinal punctures should not precede CT scanning in patients suspected of harboring an intracranial mass. The real tragedy of the lumbar puncture done on our patient (Case 3), however, was that it, too, failed to alert the physicians to the seriousness of her condition.

Signs of upper brain-stem compression such as lethargy, hyperactive tendon reflexes, partial upward-gaze limitation and large, poorly reactive pupils may be dismissed in young patients as a result of intoxication with alcohol or drugs. In particular, the presence of large but equal pupils, poorly responsive to light and often reacting better to near fixation, is an important early sign of upper midbrain dysfunction. Physicians trained to recognize the unilateral dilated and fixed pupil of a third nerve palsy caused by *lateral* transtentorial herniation may be less sensitive to the symmetric neurologic abnormalities produced by a dilated third ventricle and concomitant *central* tentorial herniation.

Obviously, careful neurologic assessment, including scrutiny of the optic discs, pupillary reactions and eye movements, is required of all patients who have recent or changing headaches. In particular, awareness of the high incidence of cysticercosis in immigrants from Latin America should lead to earlier CT scanning when such patients complain of severe or persisting headache. A diagnosis of "migraine headache" in this group should be made with reluctance.

Summary

Seven Latin American patients with obstructive hydrocephalus due to cysticercosis suffered fatal brain-stem compression. Most patients repeatedly sought medical attention because of severe headache and vomiting, as well as occasional syncope, fleeting diplopia and transient unilateral numbness. Until the moment of irreversible brain-stem compression, most were considered to have benign vascular headaches. Recognition of the high incidence of cysticercosis in immigrants from Latin America is important for the timely diagnosis of life-threatening cysticercal hydrocephalus.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Nonfluoridated Water Used in Manufacture of Infant Formulas

To the Editor: We recently read the article "Preventable Dental Disease" by Peter Rank and co-workers in the October 1983 issue.[1] We are concerned that readers may be misinformed by the statement "the increasing use of infant formulas with high fluoride content . . . ," and we wish to provide additional information on this subject.

The Infant Formula Council represents the manufacturers of infant formula in the United States. Member companies voluntarily decided in 1979 to manufacture infant formulas with nonfluoridated water based on recommendations of the American Academy of Pediatrics Committee on Nutrition.[2] Before 1979 there were various levels of fluoride in different infant formulas on the market, depending on whether they were manufactured with fluoridated or nonfluoridated water. Since the fluoride content of local water supplies varies considerably, the use of nonfluoridated water in the manufacture of infant formula allows physicians to regulate individually an infant's fluoride intake based on fluoride levels in the community water supply. Physicians can now be certain that infant formulas contain an insignificant quantity of fluoride and can safely be mixed with fluoridated water or given with a dietary fluoride supplement as medically indicated.

ROBERT C. GELARDI
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Infant Formula Council
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More on Herpes Zoster

To the Editor: As a practicing anesthesiologist for 40 years, and a specialist in pain management for the past 10 years, I am writing you in regard to the article "Clinical Aspects of Herpes Zoster" published in the November 1983 issue.[1]

Herpes zoster is, in my opinion, the most poorly treated disease in the practice of medicine. Why? Because the medical public, in general, is uninformed about the ideal treatment of herpes zoster pain, the most distressing symptom of this disease. The November article does not help in this regard. The author, Dr Glaser, does not even mention the one treatment that eradicates this pain. He obviously is unaware of it.

Conservative management consisting of corticosteroids, analgesic medication and local application of anesthetic ointment is ineffective in relieving the severe pain of herpes zoster.

Analgesic blocking has proved to be the most efficacious method of managing herpes zoster. Injection of the sympathetic and somatic nerves supplying the region involved, early in the disease—that is, within 30 days of the onset, will do three things: It will give the patient complete pain relief, it will shorten the duration of the illness and the skin eruption by 50% and most important it will prevent postherpetic neuralgia.

Only with this kind of therapy will herpes zoster give up its ranking as the most poorly treated disease in medicine.

Pain is the most important and common symptom in our treatment of human beings. Frank Moya, an internationally known professor of anesthesiology, states that at his Pain Center at the Mount Sinai Medical Center in Miami Beach, one of the largest private practice outpatient pain clinics in the United States, herpetic neuralgia is the second most common and difficult pain problem to treat, surpassed only by back pain.

Throughout the many years that I have been practicing pain management, I have seen innumerable cases illustrating the sad lack of medical information regarding the pain management of herpes zoster. Only by the correction and addition to such articles as "Clinical Aspects of Herpes Zoster" and by publishing more articles regarding the ideal treatment of this disease will we give our patients proper treatment.

ARAM FRANKLIN, MD
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* * *

To the Editor: Having recently recovered from herpes zoster and having a personal knowledge of a fairly large number of patients with this disease (mostly pediatric, it is true), I have some difficulty understanding Dr Engel's letter regarding herpes zoster neuralgia in the February issue.[1]

Unless he does a double-blind controlled study, his treatment schedule appears to have no validity. If I

had received his therapy I too could say it did wonders for me, but I used a less painful and probably much less expensive method—nothing.

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Sensitivity to Contact Lens Solutions

To the Editor: Many patients with allergic rhinoconjunctivitis are unable to wear contact lenses. This problem is frequently assumed to be due to an aggravation of their allergic problem. A case of thimerosal sensitivity is presented, which may indicate the possibility that a sensitivity to thimerosal and a contact dermatitis should be considered in allergic patients unable to wear contact lenses.

Report of a Case

A 37-year-old woman had had hay fever, urticaria and recurrent otitis media as a child. Aspirin sensitivity with generalized angioedema first developed when she was 19. Asthma was first noted at age 21 and development of nasal polyposis at age 32.

A full allergy evaluation was done at age 32. It showed a large number of very small reactions to the airborne allergens. No environmental allergies were identified. She was treated symptomatically with oral bronchodilators, nasal beclomethasone dipropionate spray and antibiotic therapy when needed for acute sinus infections.

The patient presented at age 36 with inability to wear contact lenses because of severe eye itching and inflammation. She tried both the hard and soft contact lenses without success. Although she experienced minimal eye discomfort when wearing regular glasses, a severe itchy, painful conjunctivitis would occur within two to three hours of wearing her contact lenses. Because of the pronounced exacerbation of her very mild conjunctivitis, the patient was patch tested for thimerosal and ethylenediamine. She had a notably positive reaction to thimerosal at 24 and 48 hours, with negative reactions to both control and ethylenediamine. The patient changed from her wetting solution containing thimerosal to one that contained a different preservative. She subsequently has been able to wear her contact lenses for long periods with no eye irritation.

Discussion

Inability to wear contact lenses is a frequent complaint encountered in an allergist's office and is often assumed to be related to the patient's allergies. A recent check of available wetting solutions showed most solutions contained thimerosal.

Thimerosal (Merthiolate) is an organic mercurial that is used both as a preservative and a bacteriostatic agent. It is poorly absorbed and tends to fix to the tissues.[1] Patients can have hypersensitivity reactions to either the mercurial or the thiosalicylate portion of the thimerosal molecule.[2] Tincture of Merthiolate (Lilly) also contains ethylenediamine and a number of azo dyes, all of which can be sensitizing agents.[3]

Discussion with several ophthalmologists indicates that in approximately 10% of their patients fitted with contact lenses, some intolerance to the wetting agent developed. This would be in agreement with a study that showed a high incidence of patch-test-positive reactions to Merthiolate in adults with no previous or current skin disease.[4] This case seemingly indicates that wetting solution sensitivity should be considered in allergic patients who are unable to wear contact lenses due to eye irritation.

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Have You Hugged Your Colon and Rectal Surgeon Lately?

To the Editor: A doctors' parking lot may seem an unlikely place for serious humor, but clearly it has its funny side. Consider the title of this letter for instance —a question seen recently on a bumper sticker in the lot. Or license plate tags like SYNAPSE and WHEEZE. Or PQRSTU. Yes, PQRSTU, in the middle of the alphabet. Not until its electrocardiographer author emerged did this little riddle reveal its secret.

These comic license tags give specialists identity and since we all strive for some uniqueness, we enjoy the playful touch of ego. But let's go back to the bumper sticker, for it carries an illustration of the use of humor in medical practice. While the license tags tickle our fancy, the anal/hug humor penetrates to a deeper level, even to a glimpse of serious insights. In this sense, humor and laughter can serve as powerful therapeutic adjuvants.

Hug your proctologist? In this image suggesting filth, stench, pain and mortification, we are to embrace, to hug? It is laughable. Fortunately that is what we do, that is how we handle it; we laugh at our painful predicament—together. It is therapeutic to know that—to know that we are all in this together. The laugh signals recognition of our mutual plight, for we all have animal bodies with anuses and we're stuck with them. We have to accept the givens of these biological necessities.

But the funny thing is that the comic line also tells us to test the limits of our possibilities, our hugs—even to the unlimited possibilities of love. Humor juxtaposes the necessities with the possibilities. It acknowledges our limits but encourages us to test them. So in medicine it encourages healing.

To come at this with a metaphor from an adjacent specialty, physicians serve as midwives helping people get their spirits reborn. Our very presence as medical

professionals continually reminds our patients of their inescapable, unsightly and unseemly bodily functions and dysfunctions. Our role is to help them accept and see beyond these limiting necessities to the possibilities that illness has temporarily obscured. Gentle humor can help bridge this gap. A physician using humor wisely shows both an awareness of the dual nature of humankind and a willingness to communicate in the nonscientific language of inference, symbolism and spirit. Frequently, a physician and patient can use this alternate path in addition to the hard, cold scientific facts and get a better sense of each other and of the problems and possibilities at hand. And, they can enjoy a lot of therapeutic laughter.

NEIL J. ELGEE, MD
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Seattle

The Effect of Heparin Dilution on Arterial Blood Gas Analysis

To THE EDITOR: Twenty years after Anderson[1] presented his findings on sampling and storing blood, confusion remains regarding the effects of heparin dilution on the accuracy of blood gas determinations. A commonly used text on blood gas analysis states that "if too much sodium heparin is used, it will affect the results to the acidotic side."[2] This concept is quite pervasive within medical teaching. Some studies state that excessive heparin affects the pH only minimally while arterial oxygen pressure (Pa_{O_2}) and carbon dioxide pressure (Pa_{CO_2}) may be altered more significantly[1,3]; however, the mechanism of these changes is not addressed. Clearly, there is not a wide clinical understanding of the effects of heparin overdilution on arterial blood gas measurements.

To determine what changes occur when blood is diluted with heparin or 0.9% sodium chloride solution (NS) and analyzed in the usual clinical manner we performed the following study.

Materials and Methods

Heparin sodium (1,000 United States Pharmacopeia units per ml) was added to glass syringes in volumes of 0.125, 0.25, 0.5 and 1.0 ml. Arterial blood was drawn from a patient into the syringes to a total volume of 2.0 ml. The syringes were gently rolled and tilted manually to assure mixing, and analysis of pH, Pa_{O_2} and Pa_{CO_2} was done immediately on a calibrated Radiometer ABL-2 automated blood gas analyzer. The study was repeated with arterial blood from a second patient using syringes containing only enough heparin sodium to fill the needle and hub and using NS in the same concentrations as previously used with heparin.

Results and Discussion

The results are summarized in Table 1. Upon dilution with both heparin and NS, the pH remains unchanged even in dilutions of 50%. The Pa_{CO_2}, however, falls dramatically while the Pa_{O_2} rises.

In our practice, we often observe confusion on the part of staff physicians, house officers, nurses and respiratory therapists regarding the effects of heparin dilution on arterial blood gas analysis. Most believe excessive heparin will cause the pH to fall significantly but are puzzled by the possibility of an effect on Pa_{O_2} or Pa_{CO_2}.

TABLE 1.—*The pH, Arterial Oxygen Pressure (Pa_{O_2}) and Arterial Carbon Dioxide Pressure (Pa_{CO_2}) of Arterial Blood Diluted With Heparin Sodium or 0.9% Sodium Chloride Solution (NS)*

Solution	*pH*	Pa_{O_2} *mmHg*	Pa_{CO_2} *mmHg*
Heparin Sodium	6.393	134.6	7.6
0.9% Sodium Chloride	5.900	161.4	9.4
	Percent of Initial Value		
Heparin Dilution			
6% Heparin	100	99	95
12% Heparin	100	105	92
25% Heparin	100	111	65*
50% Heparin	100	130*	38*
NS Dilution			
6% NS	100	100	98
12% NS	100	100	91
25% NS	100	105	70*
50% NS	100	112	49*

*$P < .05$.

The changes we demonstrate follow well-established principles of physics and physiology.[4] The pH, for practical purposes, remains unchanged because of the vast buffering potential of oxyhemoglobin and plasma proteins; for example, for a hemoglobin concentration of 15 grams per dl, 1.62×10^7 nm of hydrogen are required to lower the pH from 7.40 to 7.15. The hydrogen ion concentration of the heparin used in this study was 4.00×10^2 nm per liter. Hence, it would take an enormous disproportion of heparin to significantly afect the pH, much more than even a gross clinical error.

Of more practical significance, however, are the dilutional effects on Pa_{O_2} and Pa_{CO_2}. The effect on Pa_{CO_2} may be of clinical significance at dilutions of 25% or greater. The effect on Pa_{O_2} is less striking. These dilutional changes are understandable if one considers that the partial pressure of a gas in solution is proportional to the solubility coefficient of the gas and the partial pressure of the gas overlying the liquid. The Pa_{O_2} and Pa_{CO_2} of heparin or NS reflect the air/fluid boundary in the storage bottle. Hence, in obtaining an arterial blood sample one is mixing heparin with a relatively high Pa_{O_2} and low Pa_{CO_2} with arterial blood. As would be expected, the Pa_{O_2} rises while the Pa_{CO_2} drops sharply, both changes in proportion to the relative differences in partial pressure of these gases between blood and heparin.

In summary, when excessive quantities of heparin are added to blood, the primary effect on blood gas analysis is dilutional, and Pa_{CO_2} is the measurement most profoundly affected. This change in Pa_{CO_2} could lead to a misinterpretation of a patient's acid-base status. Additionally, it is conceivable that the rise in Pa_{O_2} might lead to an erroneous conclusion regarding a patient's need for supplemental oxygen. Finally, for

clinical purposes, the pH remains unaffected, even when blood and heparin are added in equal amounts. This finding may also relate to pH determinations of empyema fluid. These observations should be helpful in interpreting arterial blood gas determinations, especially in situations where only small aliquots of blood are available for analysis or carelessness occurs in obtaining a sample.

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Diagonal Earlobe Creases

To the Editor: The excellent work reported by Jorde, William and Hunt[1] found a lack of association between diagonal earlobe creases and other cardiovascular risk factors (blood pressure, smoking, weight, height, skinfold thickness, cholesterol, high-density lipoprotein, intracellular sodium, sodium-lithium countertransport and renin).

I would like to take this opportunity to comment on my own incidental observations made while conducting studies on weight gain secondary to amitriptyline maintenance in a hemodialysis population.[2] In two distinctive regards, observed earlobe creases were prominent: (1) the age of the patients was relatively young, the incidence of creases absolutely and relatively high and (2) the degree to which creases existed was great. Frequently the earlobes were divided in two with each half of the bilobe appearing spherical. Unfortunately, no simple quantitative method was devised for measuring the full range of changes observed; so a contemplated study was not carried out. This area remains open for other investigators.

The question of physiologic factors (for example, tissue fluid tides) and external mechanical factors (such as compression by a pillow while sleeping) comes to mind. Obviously anephric patients accumulate water, salt and waste products between dialyses. These are stored in the first, second and even third fluid spaces. With potassium levels high some measure of *intra*cellular as well as *extra*cellular edema could be expected.

A linear observation of my own earlobes made over a 12-year period showed them to be *un*creased at first, then later creased. The depths of my own diagonal creases were generally *not* stable, and the surrounding earlobe tissue composition likewise seemed to vary. When the substance of the lobes was engorged, the lines were deep and suggested cleavage. When dietary restriction and physical activity, on the other extreme, had led to "dehydration," the skin of the earlobes appeared loose, the diagonal lines little more prominent than many other lines that appeared locally; a deflated rubber balloon was suggested.

An additional observation made was that of easy *bruisability;* manipulation of earlobes, even though not severe, occasionally led to bruises. This was a variable finding sometimes suggested by the presence of preexisting discoloration. In my own case, bruisability came and went. The causes were not studied.

The suggestion to be found in all of these observations is that genetic, hormonal, dietary and mechanical factors all can play a role in the development of diagonal earlobe creases. The question is, do these same factors simultaneously influence the development of coronary artery disease?

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Flexible Sigmoidoscopy—A Provocative Test?

To the Editor: We are all aware of the "chandelier sign" wherein a patient with pelvic inflammatory disease leaps toward the ceiling during manipulation of the cervix on pelvic examination. We have observed a less dramatic but still impressive response during flexible sigmoidoscopy of patients sent to us with unexplained abdominal discomfort or with a tentative diagnosis of irritable bowel syndrome. Upon manipulation of the instrument or air insufflation, these patients also writhe and contort with pain. When specifically asked if this is the identical discomfort that brought them to us, or whether it is an entirely different sensation, 29 of 41 patients (70.73%) said it was identical.

We suggest that when this phenomenon is observed in the presence of a negative workup, this sign be taken as evidence for irritable bowel syndrome. We feel that flexible sigmoidoscopy should be considered not only a useful tool to exclude other diseases of the distal colon but also a provocative test in this setting because irritable bowel syndrome is primarily a diagnosis of exclusion. Additionally, a positive response is reassuring to both patient and physician.

On the other hand, lack of this sign could be produced by a spastic component proximal to the splenic flexure. Colonic spasm is frequently seen in sigmoidoscopy and appears to have no correlation with production of pain.

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Topics in Primary Care Medicine

Approach to Obese Patients

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Obesity is a common problem in North America. It occurs when food intake exceeds the energy requirement of the body for physical activity and growth. Obesity, or the amount of excess body fat, can be best defined clinically by using the body-mass index (BMI). A patient's weight in kilograms is divided by the square of the barefoot height in meters. For example, a 65-kg man with a height of 170 cm would have a BMI of 22.5 ($65 \div 1.7^2$). The normal BMI for men is 20 to 25 and for women is 19 to 24. This technique correlates closely with skin-fold measurement and radioisotope determination of fat tissue using labeled potassium. Because morbidity and mortality in a Western population do not statistically increase until the BMI exceeds 30, a patient with a BMI of 25 to 30 is classified as "overweight." Because obesity is a continuum in the human population, designations of mild, moderate or severe are artificial. For the purpose of further discussion, however, true obesity will be defined as the presence of a BMI greater than 30 and severe obesity as a BMI greater than 50, or clinically a little more than twice usual weight.

Genesis of Obesity

The causes of obesity are probably multifactorial. Damage to different areas of the hypothalamus will increase or decrease eating behavior in animals and humans. Identifiable lesions in humans, however, are rare and the existence of neuroendocrine substances that might control hyperphagia and satiety is still unproved. Obesity is clearly familial. When both parents are obese their offspring have a 75% chance of also being obese. Studies of adoped children, however, show tendencies to assume the habitus of the adoptive parents, suggesting a strong environmental influence. The adipocyte itself seems sensitive to replication through overfeeding, particularly in childhood. Persons with an excessive number (hyperplasia) of fat cells seem more resistant to weight loss than those with simply enlarged (hypertrophic) cells. Sodium pump abnormalities may contribute to obesity. Obese patients have lower adenosine triphosphatase and pump activity.

These genetic and metabolic theories together suggest a real homeostasis or "set point" of individual nutritive use, perhaps established by the time of adolescence, that tends to return persons to a predetermined point of relative leanness or adiposity. Although this homeostasis may have a protective value for an organism with varying food availability, it may also explain the difficulty in achieving long-term weight loss. Losing weight for an obese patient may be an "unnatural act." Last, issues of body image, coping, social pressure, depression, anxiety or deeper conflicts play a role in many patients to varying degrees.

The Results of Obesity

A number of metabolic changes occur from positive caloric balance and weight gain. Some of these effects associated with obesity result in the health problems listed in Table 1. These changes include type II diabetes mellitus and raised serum triglyceride and cholesterol levels. All of the above changes, coupled with increased peripheral vascular resistance, probably contribute to atheromatous disease in obese patients. Hypertension clearly correlates clinically with obesity, but the physiologic link remains unclear. Alteration of the peripheral metabolism of estrogenic substances results in men-

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TABLE 1.—*Diseases and Problems Known to Be Associated With Obesity*

Atherosclerosis
Type II diabetes
Menstrual and reproductive dysfunction
Cardiomegaly and dysfunction
Degenerative arthritis
Gout
Hypertension
Gallbladder disease
Endometrial cancer
Surgical complications

strual abnormalities and contributes to uterine cancer. Excessive weight on joints and ligaments may accelerate arthritic problems. General physical inactivity may compound cardiac problems, increase venous stasis and the risk of thromboembolism and contribute to surgical and overall mortality.

Health risks increase as the BMI exceeds 30 and severe obesity (BMI>50) carries a mortality rate 12 times the norm for patients with a BMI between 25 and 35. A number of studies, however, including the Framingham Study, have shown that being simply overweight is not a health hazard. Ironically, additional studies have shown that being slightly overweight can actually decrease overall mortality. This finding, analogous to associating the occurrence of cancer with a low serum cholesterol level, has led other observers to question the health of the study participants.

General Approach to Treatment

For a primary care clinician, treating obese and even merely overweight patients is complex, challenging and usually frustrating. Before treatment is approached, the physician must look carefully at personal biases. Many physicians dislike fat patients, perceiving them as slovenly, distasteful and lacking in self-control. Part of the success of the multimillion dollar "fat business" in America is due to the alienation that fat patients feel from their physicians. Empathy is so important in approaching fat patients that physicians who are aware of their negative feelings should immediately refer the patients to another physician who has greater interest. Physicians willing to undertake treatment of patients with weight problems should first ask if the weight loss is necessary. For patients who are not obese but simply overweight and without other medical problems, there is no clear need for weight reduction. For an overweight patient suffering from type II diabetes mellitus, hyperlipidemia, hypertension or other associated conditions, medical justification exists for treatment. True obesity, however, is a clearer indication for treatment.

Before treatment begins, a patient should first be evaluated by a thorough history and physical examination. Historical points to be emphasized include the age of onset and duration of the problem, family history, previous treatment attempts and results, current eating patterns, the use of medications such as psychotropic drugs that may increase appetite and psychologic factors.

The complete physical examination should include the blood pressure taken with a cuff of a width at least one half of the arm circumference and calculation of the BMI. Obesity-related endocrinopathy such as hypothyroidism, pituitary or gonadal dysfunction should be looked for although it is uncommon. More commonly present are diseases already outlined as associated with obesity. If the above work-up suggests another underlying or confounding disease such as thyroid disease or Cushing's syndrome, then further testing can be pursued. Similarly, the discovery of psychologic factors that stimulate or maintain obesity should result in psychiatric referral. Perhaps most important is assessing a patient's motivation to lose weight. Excess weight may be viewed with indifference by a patient or be a defense against deeper psychologic problems. If a patient does not want to lose weight, then further steps will be fruitless.

Therapy for Overweight Patients

For overweight patients, rational dietary manipulation can produce a desired result over a reasonable period of time. Positive reinforcement, such as increasing a patient's sense of well-being or lessening medical problems, is usually more effective than dire threats or embarrassment. A physician knowledgeable about caloric determination and dietary manipulation may personally undertake therapy for simple cases. If not, it is best to refer a patient to a registered dietitian who is more skilled. A reasonable plan should diminish the daily caloric intake by 500 calories, creating a deficit of 3,500 calories per week, approximating .45 kg (1 lb) of weight. Workable diets are usually determined by trial and error. The most successful diets are predicated on the awareness of what a patient enjoys eating, is used to eating and can afford to eat. For example, an "artichoke heart salad diet," seen in popular magazines, might be unrealistic on all counts for an urban Latin-American mother. A regular aerobic exercise program should be included whenever possible in all weight-loss programs. Exercise has a beneficial effect by improving insulin and lipid levels and cardiovascular fitness and shifting catabolism from protein to adipose tissue. Regular exercise may even accelerate resting metabolism beyond the exercise period and generally improves a patient's sense of well-being.

Because permanent weight loss depends on a permanent change in eating habits, behavior therapy has become popular. Behavior therapy depends, in its simplest form, on peer pressure, gentle competition and group support. Groups that use aspects of this philosophy include Take Off Pounds Sensibly (TOPS) and Overeaters Anonymous (OA). Although patient attrition may be as high as 50% in the first two months, these groups offer usually inexpensive general diet programs and psychologic and social support. A more complex form of behavior therapy is behavior modification. Although components vary considerably in individual programs, they hold several themes in common. First, the patient self-monitors body weight, food

intake and feelings about eating. Second, there is implicit or explicit goal setting and, third, rewards or punishments are given. These components are reinforced through therapist, group or family support. On the positive side, behavior modification programs offer a rational integration of personal and environmental control of eating and seem to improve diet compliance. On the negative side, their "prepackaged" nature can make them insensitive to the complex psychologic differences of individual patients.

Physicians also have an obligation to protect patients from irrational and dangerous drugs and diets. Anorectic agents if used at all should be limited to brief periods and only as part of a more comprehensive program. Only the newer agents such as fenfluramine hydrochloride or diethylpropion hydrochloride with low abuse potential should be used. In contrast, thyroid medication is dangerous and the use of diuretics is irrational. Fad diets are so numerous that informed physicians need to depend more on popular literature than traditional medical journals. As a guideline, diets requiring restrictions of less than 1,000 calories a day require medical supervision. Low-calorie diets coupled with a dominance of one food type such as high fat, high protein or all fruit are unbalanced and ultimately intolerable. And, finally, all rational diets should offer a livable maintenance program that extends beyond the "guaranteed" period.

Treatment of Obesity

Truly obese patients need to be approached differently. Simple dietary manipulation and motivation usually have been tried repeatedly with minimal, transient results. Unless a primary care physician has had special training, it is best to refer obese patients to a reputable specialist such as an endocrinologist or bariatrician. There are two general avenues of therapeutic approach, medical and surgical. Behavioral therapy or even psychotherapy must also be integrated into both if any success is to occur.

Because obesity is a continuum, a well-motivated patient with mild obesity (BMI of 30 to 35) might succeed with the overweight plan just outlined. If not, intensive medical therapy should be tried first. For a moderately or severely obese patient, this means a diet of 800 to 1,000 calories a day maximum. Adequate protein must be provided to prevent malnutrition. The best known reputable diet is the protein-sparing modified fast. A patient's fast is supplemented with 70 grams of vegetable or animal protein and 800 total calories as well as vitamins and minerals. The protein is of a high biologic value and unexplained deaths previously associated with the low-biologic-value liquid-protein diets have not occurred. Each patient must be followed carefully by physicians and dietitians and regular laboratory testing done for serum glucose, potassium, urea and uric acid levels. Metabolic symptoms are usually transient and minor electrolyte disturbances are corrected through supplements. A number of low-calorie programs similar to the protein-sparing modified fast have recently evolved. Most of them vary in percentage of protein, carbohydrate and fat, but at least 0.8 grams of protein per kg of body weight per day should be provided. Behavior modification is taught throughout the fast as well as transition feeding techniques when the patient terminates the fast and returns to more conventional food. Follow-up must be diligent and long-term.

The role of surgical intervention in the treatment of obesity remains controversial; intervention can be effective but problems are common. The jejunoileal bypass is almost 30 years old and produces a significant weight loss through both malabsorption and decreased oral intake. Follow-up studies beyond five years, however, show important complications such as persistent diarrhea, kidney stone formation, hepatic pathology including cirrhosis and failure, gallstones, nutrient deficiencies and major psychologic problems. These complications eventually afflict more than half of the patients and commonly require reanastomosis. Only 30% of patients have had no major problems, maintain moderate weight loss and are content with the results. This procedure's high failure rate and continuing morbidity and mortality today preclude its general use.

The past decade has seen the evolution of a different surgical procedure for obesity, the gastric stapling or bypass. This procedure is anatomically analogous to a partial gastrectomy and produces weight loss similar to the intestinal bypass but without the metabolic complications. Technically more difficult than an intestinal bypass, surgical complications may occur. Because a smaller stomach pouch is created, persistent vomiting may occur. This procedure should only be undertaken by skilled surgeons dedicated to intense follow-up. Patients should be reasonably intelligent, agree to protracted follow-up and give consent after the risks, known benefits and therapeutic options have been carefully explained.

Results of Treatment

Weight loss is easy to initiate but successful completion and maintenance are very difficult for a number of reasons. First, patients' initial enthusiasm for a new diet is gradually replaced by the growing tedium of living with it every day. Second, human adult behavior, though malleable, is very difficult to substantially remodel over long periods of time. Third, normal weight homeostatic mechanisms, already discussed, counter even the most aggressive diet. Last, too little is known about the types, physiology and behavior of obesity to plan truly individualized therapy.

There is an inverse relation between the degree of obesity and the success of therapy. Therapy for overweight, therefore, has the best chance for initial success. Up to 30% to 60% of patients are able to lose 9 kg initially, though many regain it after a year. Behavior modification has aided the problem of maintaining weight loss. Recent studies suggest that after one

year 70% of all patients may maintain or continue to lose after an initial loss of 7 kg.

Results of intensive medical therapy, usually reserved for more obese patients, reflect the refractory nature of the problem. Although the protein-sparing modified fast diet results in an initial average weight loss of 18 kg, only a third of the patients are able to maintain the loss over two years. The gastric bypass can produce an initial weight loss of 40 kg but few studies go beyond two years.

Summary

The treatment of obesity remains unsatisfactory. Overweight, motivated patients should be treated if responsive medical conditions coexist. Truly obese patients need to be treated because of the associated health risks. Rational dietary manipulation coupled with exercise and behavior therapy offers the best total program for overweight and mildly obese patients. For the moderately to severely obese patients, intensive medical therapy with a protein-sparing low-calorie diet and intensive behavior therapy is a first recommendation. Gastric bypass is the current surgical procedure of choice following unsuccessful medical therapy. In conclusion, although we can speak of overweight as a curable condition, true obesity remains a lifelong problem that will continue to tax the ingenuity, courage and perseverance of researchers, clinicians and patients for years to come.

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Health Care Delivery

A Statewide Approach to Health Care Personnel Maldistribution

The California Area Health Education Center System

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An Area Health Education Center (AHEC) system has been established in California to address the maldistribution of physicians and other health care professionals. The AHEC program uses educational incentives to recruit and retain health care personnel in underserved areas by linking the academic resources of university health science centers with local educational and clinical facilities. The medical schools, working in partnership with urban or rural AHECs throughout the state, are implementing educational programs to attract trainees and licensed professionals to work in underserved communities. The California AHEC project entered its fifth year in October of 1983 with the participation of all eight medical schools and the Charles Drew Postgraduate School of Medicine, 35 other health professions schools, 17 independent AHECs and more than 400 clinical training sites. Educational programs are reaching more than 22,000 students and practicing health professionals throughout California. We review the current status of the California AHEC system and use the AHEC programs at Loma Linda University to illustrate the effect this intervention is having.

(Crowder JE, Schnepper JE, Gessert C: A statewide approach to health care personnel maldistribution—The California Area Health Education Center system [Health Care Delivery]. West J Med 1984 May; 140:798-802)

An Area Health Education Center (AHEC) system has been developed in California to address the maldistribution of physicians and other health care professionals. The AHEC program uses educational incentives to draw together and support health care personnel in underserved areas. In California this is being accomplished by organizing all the medical schools and their respective community-based AHECs into a partnership. The California AHEC system is midway through its nine years of funding. Over the next four years this support will be decremental, as dictated by federal policy. Other sources of support will be needed if a public service program such as this is to continue in California. We review the California AHEC's organizational development and approach to improving the geographic distribution of physicians and other health care personnel.

In the early 1970s the Report of the Carnegie Commission on Higher Education supported the view that AHECs could be valuable in improving the quality of health care and overcoming problems of health professions maldistribution.[1,2] By the mid 1970s several studies indicated that the increased number of rural primary care physicians in some states was due to the presence of AHECs.[3]

Clinical experiences in rural areas and medical stu-

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ABBREVIATIONS USED IN TEXT

AHEC = Area Health Education Center
LLU = Loma Linda University
UCSF = University of California, San Francisco

dents' increased awareness of rural needs were also shown to be factors influencing physicians' decisions about practice location.[4] To motivate health professionals to settle in underserved areas, two major federal programs stand out among the many that have been established: The National Health Service Corps, which provides scholarships in return for an obligation to practice in an underserved area, and the AHEC program. Together these programs are working to balance the geographic distribution of health care personnel.[5]

Since its inception, many states have benefited from the AHEC concept, as noted by greater retention of health care professionals.[6] For example, with AHEC support the University of Colorado established a physician inventory for identifying areas with a shortage of health professionals and assessing the degree to which areas of the state are medically underserved.[7] This has contributed to increased physician awareness of shortage areas and has been successful in supporting decentralized medical education by the use of student clerkships and preceptorships.[8]

The AHEC program in California began in 1972 when the University of California was awarded funding for a program to be conducted in the Central San Joaquin Valley. Both the University of California at San Francisco (UCSF) (where the federal contract was administered) and the University of California at Los Angeles contributed academic resources and support to the AHEC. Programs provided for developing and expanding medical student training in the San Joaquin Valley and enhanced local programs in nursing, pharmacy, allied health and dentistry. A continuing education network was developed for a great expanse of the valley; library and learning-resource programs were brought to many of the hospitals in the target area. Because of the program's success in recruiting and retaining physicians, nurses and other health care personnel in underserved areas, it has been used as a model for AHEC programs elsewhere.[9]

In the fiscal year 1978-1979 UCSF, acting on behalf of the Regents of the University of California's five medical schools and California's three private medical schools, applied for and was awarded funds to begin a statewide AHEC program. The proposal was developed in response to a revision in AHEC legislation calling for the establishment of statewide programs to take a more comprehensive approach to the problem on a fund-sharing basis. The California AHEC system accepted the role of providing leadership in the state by coordinating and facilitating programs for local needs through existing health professions schools.

Organizational Strategy

The goal of the project parallels that expressed in Public Law 94-484: "For the purpose of improving the distribution, supply, quality, utilization, and efficiency of health personnel in the health services delivery system."[10]

To accomplish this goal, the California AHEC system has implemented a detailed, far-reaching strategy. Under contractual agreements each participating medical school is responsible for the planning, development and contractual support of one or more AHECs. The AHEC, in turn, is responsible for working with the academic health science center to provide and support educational programs in the underserved area represented by the AHEC. Finally, the community-based AHEC is to represent the interests of the consumers, individual providers, the institutions providing health care and educational resources in its defined target area.[11]

To establish an effective statewide project a comprehensive plan for the organization was developed. The program invited the eight fully developed medical schools and the Charles Drew Postgraduate School of Medicine, as well as other health professions schools, to be part of the project network. It established working relationships with several key agencies in California such as the Office of Statewide Health Planning and Development, the Health Systems Agencies, the California Postsecondary Education Commission and the Health Manpower Policy Commission. Furthermore, as required by law, a Statewide Program Advisory Committee, representing a variety of constituencies, was organized. The Council of Regional Directors, comprised of representatives from the participating medical schools, was created to coordinate project activities within the respective regions of the state.

Program Objectives

The AHEC program can address a wide range of educational needs. Priorities are established through input from representatives of the target area, by the participating schools and by the federal AHEC legislation. Although activities may be tailored to meet urban or rural populations, all California AHECs have common objectives, such as the following: "A fundamental focus of program activity will be the network of affiliated primary care physician residency training programs, especially family practice. The plan of every AHEC will include activities and resources to add adequate strength to a primary care residency training program and to expand that program or extend its reach to more underserved areas." (California Area Health Education Center System Cooperative Agreement Application, July 1, 1981, through June 30, 1982. Submitted to the Bureau of Health Professions, Health Resources Administration, by the Regents of the University of California.)

Another objective involves the training site of under-

graduate medical students. By the end of the third year, each participating school must certify that 10% of its clinical instruction is conducted in AHEC target areas through an undergraduate medical education program of clerkships and preceptorships that is supported by its affiliated AHEC(s).

AHEC resources are also used to support training programs for associated health professionals such as dentists, nurse practitioners, physician assistants, clinical pharmacists and nutritionists. Another ingredient in every AHEC program is the Health Professions Career Opportunity Program, with the goal of increasing the recruitment and retention of health professionals from minority or disadvantaged communities. These persons can then serve as role models and attract other members of their community into the health professions.

All of the various AHEC-supported programs can be coordinated to share faculty and facilities, contributing to an optimum environment to promote interdisciplinary clinical training.

Program Results

In October 1983 the California AHEC system began its fifth year. Because each center goes through a full year of planning and another year of development before becoming fully operational, this means that most mature centers in the California AHEC system had been operating for two years by October 1983. A major accomplishment of the California AHEC system has been the developing cooperation and partnership among the eight medical schools, the Charles Drew Postgraduate Medical School, 35 health professions schools, 17 independent AHECs and more than 400 clinical training sites. The communities believe the AHEC program helps to recruit and retain health care practitioners. Student trainees learn primary care skills appropriate for practice in underserved areas and become familiar with communities where their skills are needed. Practicing physicians, dentists, nurses and other health care professionals appreciate the AHEC-supported continuing education programs to help alleviate problems of professional isolation.

The following is a brief review of the areas of educational instruction occurring within the California AHEC system.

Undergraduate Medical Education

Each year more than 2,000 third- and fourth-year medical students have an opportunity to participate in AHEC-supported training programs through the more than 31 academic departments of the participating medical schools, 36 community hospitals and 140 community clinics, National Health Service Corps sites and small clerkship sites. The AHECs support programs provide for more than 9,400 student-weeks of clinical education in the target areas of the California AHECs. For example, AHEC support has facilitated the development of an entirely new required clerkship in family medicine for medical students at Loma Linda University (LLU), as well as an additional clerkship site in pediatrics in the target area away from the university's tertiary care medical center.

Graduate Medical Education

The 17 developing and operating AHECs provide support to a total of 29 primary care residency programs. These programs are based at 23 hospitals throughout California and reach out to 71 community clinics and community-based training sites. At the LLU-affiliated residency program in family practice at Riverside, the AHEC sponsors a nutrition specialist to teach resident physicians how to do brief nutritional assessments and office counseling regarding dietary aspects of health and illness.

Furthermore, 79 practicing physicians and fellows are enrolled in faculty development programs supported by AHEC and Song-Brown funds from the State of California. The objective of this program is to enrich the supply of well-qualified family physicians for practice in California.

Nursing Education

More than 550 students are participating in AHEC-supported programs associated with 22 schools of nursing, based at both community college and baccalaureate-level schools in California. In these programs, students have the opportunity to achieve a nursing degree at three levels, Associate (ADN), Bachelor of Science (BSN) and Master of Science (MSN). At LLU a learning assistance program was instituted to improve the study habits and test-taking skills of academic underachievers. Nursing students from LLU and other schools of nursing in the Riverside-San Bernardino area are eligible to participate in the program. The AHEC also provides for about 18 students to participate in preprofessional training programs.

Dental Education

A total of 511 third- and fourth-year dental students and 221 hygienists and dental assistant students from four California schools are participating in programs in six AHECs and six clinics. Clinical experience can be acquired in dental outreach in underserved communities, with the intention of providing students with opportunities to work with specific underserved populations, such as the inner-city poor, rural farm workers and elderly patients. The LLU School of Dentistry operates two dental education programs for training third- and fourth-year dental students in decentralized rotations throughout the LLU-affiliated AHEC target area. These programs include experience in geriatric dentistry and elementary school age dental screening.

Pharmacy Education

Several AHECs in California support the involvement of clinical pharmacists as faculty in family prac-

tice and other primary care residency programs. In addition, three schools of pharmacy cooperate with seven AHECs to provide pharmacy students training experiences at ten different community sites. Statewide, 90 senior pharmacy students are in clinical training in the AHEC programs and 151 practicing pharmacists will be enrolled in a series of miniresidency programs leading to postgraduate certificates.

Nurse Practitioner and Physician Assistant Programs

Four nurse practitioner and four physician assistant programs receive AHEC support, enabling the trainees to acquire clinical training in more than 45 facilities removed from their major teaching campuses. Sites include eight community hospitals and more than 37 community clinics and National Health Service Corps locations in underserved areas. A total of 333 nurse-practitioner trainees and physician-assistant trainees will receive training in the fifth year of the California AHEC project.

Allied Health and Other Disciplines Education

In all, 52 students are participating in allied health programs supported by AHECs, including 8 medical technologists, 22 dental hygienists and 10 dental assistants. A total of 56 other allied health students will be trained as paramedics and emergency medical technicians. These programs include classroom instruction and clinical training, giving the students exposure to the health care needs in rural and underserved areas.

Health Education and Nutrition

AHEC-supported training programs in health education and nutrition reach 1,635 students at 21 hospitals and clinics, eight medical schools and two colleges. At LLU and in several other settings, clinical instruction in health education and nutrition counseling is included in the curriculum of primary care residency programs.

Continuing Professional Education and National Health Service Corps

The goal of continuing professional education is to bring educational resources to remote settings, including National Health Service Corps sites, so as to decrease the professional isolation of the health providers in such communities, thereby improving their retention where they are most needed. During the fifth year of the California AHEC project, it is projected that there will be more than 10,900 contact hours of AHEC-supported continuing professional education programs offered through 53 hospitals, 8 colleges and other community sites. In addition, about 160 professionals working for the National Health Service Corps will also be offered such courses at 15 corps sites and three hospitals. Through Loma Linda University, several on-site continuing education programs in rural or isolated areas have been conducted, with special emphasis on the needs of the National Health Service Corps personnel and primary care physicians and nurses. At LLU there are now 23 remaining National Health Service Corps obligees enrolled in medical school and recently the university hosted a statewide information workshop for all medical students and resident physicians in southern California funded by the National Health Service Corps.

Minority and Disadvantaged Recruitment and Training for Health Professions Career Opportunity

More than 2,000 students in 21 colleges, 62 high schools and other community settings have the opportunity to learn about a career in the health professions through AHEC-supported health clubs, tutoring, counseling and workshops or seminars. The instructional process also takes place through orientation programs, career fairs and classroom visits by minority health professionals, who provide role models for future professional school applicants.

Library/Learning Resources

AHEC-supported library/learning resource programs provide ongoing medical information to hospital libraries by making major medical libraries more accessible to outlying hospitals. Hospital personnel can thus receive assistance on information not readily available in their own hospital library. Almost 600 hospital medical librarians and related people will receive instruction at workshops and seminars conducted by AHEC library program staff. At the LLU library, the AHEC Library/Learning Resources Program has been developed to integrate the small urban and rural medical centers into a regional information-processing system. This program is being used to expedite the processing of professional journals, books, tapes and computer literature searches (MEDLINE) to hospitals and clinics that have not previously had this service available.

Discussion

One of the most remarkable results of California's AHEC project has been the spirit of cooperation seen among the medical schools. Historically, there has been little joint program development among California's medical schools; as part of the California AHEC system, the schools are working together to achieve a common purpose. Under the skilled leadership of Malcolm S. M. Watts, MD, Project Director, and the capable day-to-day management of Associate Project Director Clark Jones, most major decisions are made not by majority vote of the Council of Regional Directors but rather by consensus following a thorough discussion of the issues. Most important, the California AHEC system has been successful in developing educational linkages between health science centers and communities. As the project enters its fifth year, this balanced partnership continues to significantly benefit

both health science centers and underserved communities.

In conclusion, the California AHEC system's programs have been developed to encourage medical students, physicians and other health care personnel to work in medically underserved areas. The California AHEC project is striving to achieve its goal of stimulating health professionals to select such sites for training and future practice, and to better prepare them to meet the health care needs of underserved populations.

As the California AHEC system looks to the future, the centers and the communities they serve, the participating health professions schools and the system as a whole must examine the ongoing needs for community-based education programs for the health professions in California. If enough centers identify ongoing community needs and an interest in continuing the California AHEC system, new sources of funding will be required.

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Medical Schools of the West

University of Washington School of Medicine

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The progress of the University of Washington School of Medicine (see Figure 1) and the history of Seattle and the Pacific Northwest are inextricably intertwined. Just before the Civil War, the first territorial legislature decided the territorial capital should be established in the settlement of Olympia and Seattle should become the home of the University of Washington. The first, but ineffective, step to establish a school of medicine was taken in 1878, when the president of the university named a three-doctor committee to investigate the matter. The regents adopted the committee's report and so did the legislature. However, the funds were not appropriated and the proposal languished.

University President Henry Suzallo proposed a three-step plan: make the premedical course second to none, postpone indefinitely establishing a school of medicine and establish a postgraduate medical lectureship under the auspices of the local medical society and the university. Year by year, preclinical studies were added to the general university course list, including anatomy and hygiene, the precursor of public health. Nursing and pharmacy were established as university professional schools.

King County Hospital (now Harborview Medical Center), which opened in 1931, became well known as a teaching center for housestaff well before the School of Medicine was founded. Toward the end of World War II, a few doctors thought the time was finally right to create a school of medicine. The state's coffers were filled with sales taxes collected during a booming economy.

Dr Paul Sieg, president of the University, suggested the simultaneous planning for a dental school and also that facilities and faculty required in common be a joint enterprise between the new schools.

Legislation establishing schools of medicine and dentistry was signed on March 1, 1945—67 years after the Board of Regents approved the recommendation of the first committee that suggested the founding of a medical school.

Edward L. Turner, MD—Founding Dean

The next task was to find a dean. Of the dozen or so persons considered, the one who appeared most promising was Dr Edward L. Turner.

Dr Turner was a physiologist and physician who had taught in Lebanon at the American University of Beirut and had served as president of Meharry Medical College in Nashville, Tennessee. In 1945 Dr Turner came to Seattle and accepted the challenge of building a medical school from the ground up. Within 11 months he welcomed the first entering class at the University of Washington School of Medicine.

Dr Turner sought energetic leaders in basic scientific research from within and outside the University of Washington. He felt he could recruit the first students and within two years or so have the clinical departments organized to take care of the junior and senior years. Makeshift quarters—attics, basements, temporary buildings—were immediately put to use for the new school (see Figure 2).

In December 1945 the Board of Health Sciences was established, including the four health sciences deans (medicine, dentistry, nursing and pharmacy), the dean of the graduate school, the dean of the college of arts and sciences and the head of chemistry. They met to discuss matters of joint concern such as new faculty appointments, common services such as the library and the vivarium and the design of the proposed Health Sciences Building.

The University of Washington had by that time

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moved from its original downtown site to its present one on 600 acres in the northeast part of the city. It continued to own its original 10-acre site in what is now Seattle's financial district and to lease the buildings there. This so-called "Metropolitan Tract" figured prominently in the financing of University Hospital.

Establishing Goals

Dr Turner knew the original sum appropriated to establish the dental and medical schools would not provide a satisfactory building and he urged the planners to design an ideal complex, with the assumption that financing could be found. It was. As completed in 1949, the Health Sciences Building cost $10 million.

Other goals enunciated by Dr Turner in his first few weeks included an emphasis on keeping the course of study as integrated and divorced from departmental rigidity as possible, and constant reevaluation of what was taught and how much was essential, objectives that continue to this day.

One of the main goals of the first faculty and, in fact, the primary concern of the first dean, was to attract teachers and scientists of the greatest ability. The research record of each candidate for a faculty position was scrutinized more closely than honors received or the titles of previous assignments. A concomitant effort was made to enroll top students interested in obtaining the best medical education.

In the clinical sciences, Dean Turner insisted on having the university's own teaching hospital on campus directly adjoining the faculty offices and research facilities, but it took 14 years for this to become a reality. In the meantime affiliation agreements, which have become a vital part of the clinical program, were successively reached with King County Hospital (now Harborview Medical Center), the Marine Hospital (now the Pacific Medical Center), the Veterans Administration Hospital and Firland Hospital. To date, almost 4,500 interns and residents have been trained in the university program.

As the affiliations fell into place and clinical teaching proceeded, Dean Turner's thoughts increasingly turned to the on-campus teaching hospital he regarded as a prime necessity.

The 1949 legislature authorized the university to pledge its own building funds up to $2 million and

Figure 1.—The University of Washington School of Medicine is a component of the Health Sciences Center. The mammoth health sciences complex, which is more than a quarter mile in length, is framed by Portage Bay to the south and the main campus of the University of Washington to the north.

placed the $20 million capital needs of all higher education (about half for the hospital) on a statewide referendum. The referendum failed by one third of 1%. Efforts were renewed at the 1951 session.

Despite the setback, an eloquent tribute to the school came from two very well-informed visitors, the accreditation team representing the American Medical Association and the Association of American Medical Colleges:

> The greatest credit is due the administration and faculty of the University of Washington School of Medicine for the manner in which they have created . . . in five years an institution that promises to become one of the outstanding medical schools of the world. Particular credit is due Dr Turner . . . for the imagination and broad vision that has characterized his leadership and for the courage and resourcefulness with which he has faced and overcome serious problems.

In 1953 Dean Turner resigned to become the secretary of the Council on Medical Education of the American Medical Association in Chicago. He felt that the fresh view of a new dean might do a lot to solve some of the remaining problems, particularly those of acquiring the teaching hospital.

Work was by then under way on the first unit of the teaching hospital made possible by prior authorizations and federal matching funds. It contained headquarters for the hospital administration and offices and laboratories for the clinical departments, but no patient beds. The authorization and building of the rest of the teaching hospital remained the most formidable task at hand.

James W. Haviland, MD—Acting Dean

Asked by University President Henry Schmitz to suggest persons to be named acting dean and permanent successor, Dr Turner unhesitatingly recommended Dr James W. Haviland for both. Characteristically, Dr Haviland chose only the former.

A native of Glens Falls, New York, Dr Haviland had first come to Seattle in 1940 with the State Department of Social Security and he returned to Seattle to set up practice after serving in World War II. Although informally in touch throughout the entire development of the medical school, Dr Haviland, an internist, agreed to take the post of assistant dean on a part-time basis in 1949. He became acting dean in 1953. Active in his specialty societies and in the Washington State Medical Association, he was to prove an indispensable link in interpreting the school to the practicing community and the other way around.

Of the prevailing attitude among his fellow practitioners, Dr Haviland said

> We wanted a good school, but at the same time I think we were all a little concerned . . . it might pose a threat to the practicing community if it were not run properly with an eye to the needs of Seattle and its patients. I was able to give Ed Turner fairly constant access to the board of trustees of the State Medical Association and county medical society and let him work with the officers to draw fairly formal agreements about how the school's practice plan would function.

Dr Haviland recalled the evening meeting where town and gown met to "thrash things out . . . sometimes with a lot of name-calling."

But "Ed Turner took a lot of time to make sure the school started off properly" and encouraged his department chairmen to do the same.

When named acting dean, Dr Haviland took the appointment on a half-time basis and maintained his practice. It is probably more accurate to say Dr Haviland

Figure 2.—The Department of Medicine had its beginnings in 1948 in an abandoned army barrack behind Harborview Medical Center in downtown Seattle.

gave full time to the dean's office and half time to his practice.

The Board of Regents revised its stand on a $5 million bonding authority based on the future income from the University's Metropolitan Tract in downtown Seattle. With available Hill-Burton Funds, other federal grants and university building funds, there was enough money in sight to make it reasonable to go ahead with faculty and architectural planning and to consider building a University Hospital.

"With that in mind," Dr Haviland said, "I went to the university administration and in my brashness talked to Henry Schmitz and said it was going to be possible to fund the hospital and I asked permission to go ahead with the design of University Hospital. So we got busy and I think that was a godsend."

George Aagaard, MD—Second Dean

The search for a permanent second dean ended when Dr George Aagaard accepted the post in 1954. The acting dean, Dr Haviland, stayed on for several years as assistant dean to help Dr Aagaard during the transition and has since served the school in a number of capacities.

When he arrived on campus the new dean was impressed with the progressive ideas evident at the new school. "Here was a chance to help build a great medical school," recalled Dr Aagaard, who came to Seattle from the deanship of Southwestern Medical School at the University of Texas. Now Distinguished Professor of Clinical Pharmacology at the school, he has deep admiration for the school where he has now spent more than 30 years of his career.

"When I came here," he said, "the school already had an outstanding faculty and imaginative programs. The founding dean had brought in a number of talented teachers and researchers, all hard workers."

He was attracted to the UW medical school, Dr Aagaard said, because it was an integral part of a state university, and he always felt the chance of developing a truly great medical school was best if it was located on the main campus of a university. However, at the time he assumed the deanship, working conditions for the faculty and administrators were difficult. The principal deficiency was that the school did not have a teaching hospital of its own.

The faculty, however, did more than make do. It created residency training programs at the affiliated hospitals that attracted the top graduates from around the country, some of whom were destined to become the leaders of the medical school in later years. In turn, the faculty encouraged the first classes of medical students from the UW School of Medicine to "leave the nest" and compete for residencies at respected training programs nationwide, thus enhancing the name of the school.

"The faculty felt it was good for people at other teaching hospitals to see the quality of education of graduates of the University of Washington School of Medicine," Dr Aagaard said. At the same time, the school became known internationally for the research excellence, both basic and clinical, of its faculty. The school's success in research perhaps can be measured by the ability of its faculty to attract millions of dollars for research from the National Institutes of Health and other public and private sources.

During Dr Aagaard's tenure as dean the faculty continued its tradition of reviewing the curriculum constantly and modifying it frequently. He noted that there were two major revisions of the curriculum during his ten years as dean, and a third was launched before he left.

"The faculty was and is heavily involved in research, yet concerned with the quality and vigor of the medical student's education," Aagaard observed.

University Hospital

In 1956 the university began construction of University Hospital (see Figure 3). Originally conceived as a 16-story, 600-bed institution, lack of funds forced the building of a hospital half this size. In 1959 the hospital opened and admitted its first patients. Although among the smallest of teaching hospitals, its reputation as an excellent place to receive care grew rapidly. Within two years after it opened, University Hospital was chosen as one of the first hospitals to receive funding from the National Institutes of Health to establish a Clinical Research Center (CRC) in one of its units. The CRC was the first in the nation to receive patients; now more than 200 such centers are active in hospitals across the country. Many patient care advances spread from University Hospital and the School of Medicine to the rest of the world.

University Hospital has begun its first major expansion in 24 years and will grow from 336 to 450 beds, an event the man who was dean when the hospital was built regards as "wonderful." Because the hospital cares for patients from throughout the Pacific Northwest and Alaska, he said, the additional space will help, in part, to meet the regional need for patient care, as well as providing a more spacious training ground for medical students.

Diversity

The availability of multidisciplinary facilities in addition to hospitals at the University of Washington has also contributed to the school's success, according to Dr Aagaard.

"The more diversity you have, the more likely you are to bring people to the school who have a particular interest or expertise," Dr Aagaard said. His list of those who came to the school to set up individual programs reads like an honor roll of scientific and medical luminaries. Dr Aagaard gave a few examples: Ruch, the national expert in primates who established the Regional Primate Research Center; Blandau, who per-

formed and encouraged basic research in reproduction; Bruce, who developed exercise protocols in cardiology used throughout the country; Rushmer, another expert in cardiology and bioengineering; Finch, the first head of hematology who did definitive work on iron metabolism; Ripley, the first chairman of psychiatry who catapulted the department to world prominence, and Ward, the noted neurosurgeon and epilepsy researcher who founded the Department of Neurological Surgery. The list goes on and on, said Dr Aagaard, who is himself prominent in hypertension research.

John R. Hogness, MD—Third Dean

In 1964 Dean Aagaard unexpectedly announced that he felt ten years was a sufficiently long time for a dean to serve and that he wanted to remain as a professor of medicine. He recommended Dr John R. Hogness as his successor. The recommendation was promptly accepted.

Dr Hogness had originally come to Seattle to be chief resident at Harborview Medical Center. He later completed a fellowship with endocrinologist Dr Robert Williams, the founding chairman of the Department of Medicine. Hogness practiced for a time in downtown Seattle, but then relinquished his doctor's office to become the first medical director of University Hospital and later associate dean of the medical school under Dr Aagaard.

"Aagaard contributed immensely to the growth of the school," Dr Hogness said. "A spirit of excellence developed, and a number of new buildings went up."

Dr Hogness became dean during medical research's heyday:

> Budgets grew tremendously. It was a fun time. In fact, the job of dean of the School of Medicine was the most fun of any job I've had. It's easy to administer a school when it is thriving, when there is cooperation among faculty, when they are piling up accomplishments, when a solid reputation is being built.

Personable, easygoing and known for his sense of humor, Dr Hogness was at the same time a capable and businesslike administrator. With insight gained because he came from the practicing community, Hogness was able to resolve the town-gown conflict between the School of Medicine and local physicians and hospitals. He invited practicing physicians to serve on the school's committees.

Dr Hogness also requested changes in the curriculum in the fall of 1967. The men chosen to carry out these revisions were Dr John Sherris and Dr August Swanson. A few years later, when Dr Hogness accepted another position at the University of Washington, Dr Swanson was named acting dean.

In the meantime, Hogness became the first director of the university's newly formed Health Sciences Center in 1970. He later resigned to become president of the Institute of Medicine of the National Academy of Sciences in Washington, DC.

At the end of his term as president of the Institute, Hogness returned to Seattle to serve as university president for a number of years. He is now president of the Association of Academic Health Sciences Centers,

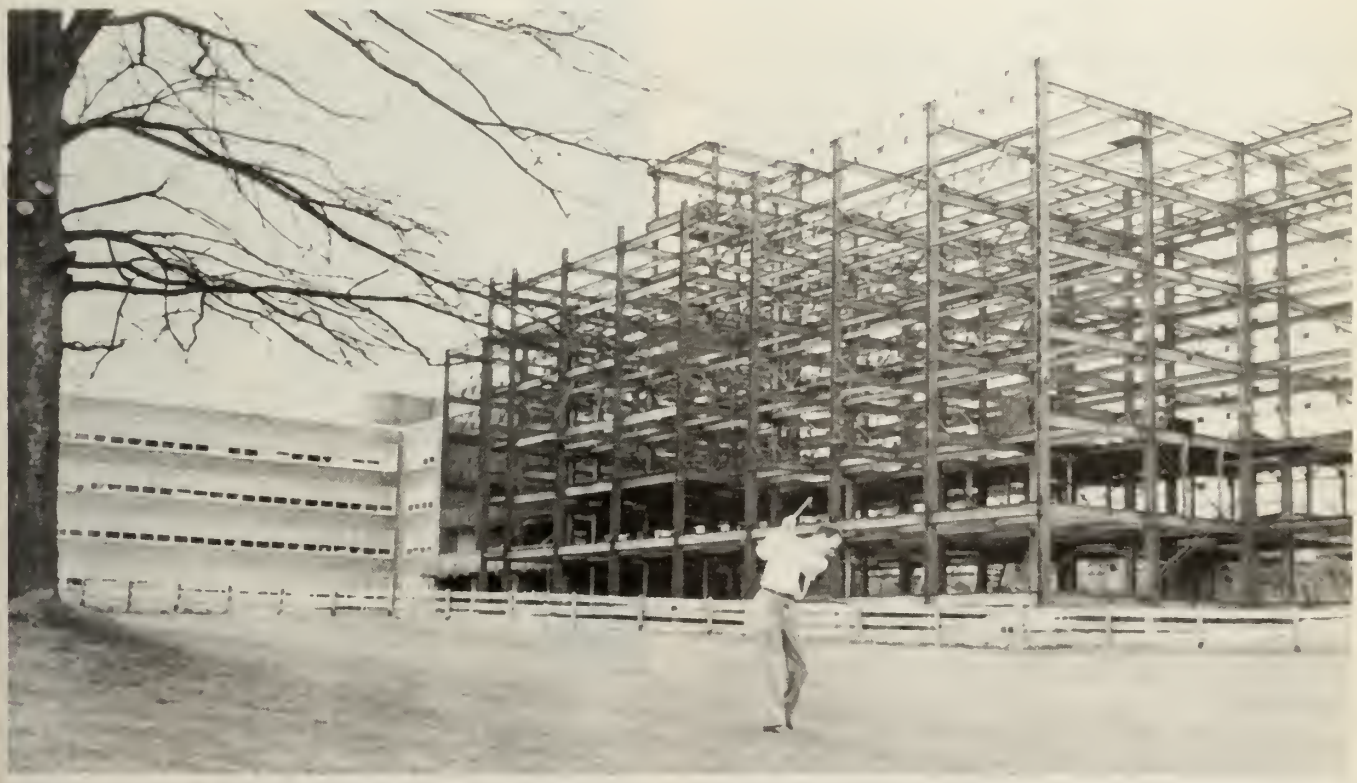

Figure 3.—The University of Washington Health Sciences Center was built on a golf course. The demise of the golf course occurred in 1956 when University Hospital was constructed. Above, a golfer enjoys one last game.

which represents the health sciences complexes of major universities in North America.

August Swanson, MD—Acting Dean

Dr August Swanson, the man who filled the role of acting dean after Dr Hogness left the school, was able to build on the work of his predecessors and achieve a balance between education and research at the school. "The school continues to do phenomenally well in meeting these two challenges," Dr Swanson said recently.

Dr Swanson was one of the first interns at the School of Medicine. He joined the faculty to head a new program in child neurology. In 1967 he was asked to serve as associate dean for academic affairs because, in his words, he was "an old hand" at the school.

Dr Swanson recalled changes in the curriculum made in the late 1960s to strengthen the school's educational programs. In 1968 the school reduced the scheduled hours of required course work and encouraged students to pursue independent study. Some took electives on other parts of campus. Different methods of teaching were offered to suit different learning styles of the students.

"This effort worked partly," he said, "but it was difficult to divorce ourselves from the philosophy that we have to teach rather than educate." Dr Swanson did, however, make tremendous inroads in revamping and modernizing the curriculum.

Dr Swanson is currently director of academic affairs of the American Association of Medical Colleges and is project director for the AAMC's effort to define the general education of physicians.

Robert L. Van Citters, MD—Fourth Dean

In 1970 Dr Robert L. Van Citters, the school's associate dean for research and graduate programs, became dean. A graduate of the University of Kansas, he had come to the University of Washington as a special research fellow supported by the National Institutes of Health's Cardiovascular Training Program. Later he received faculty appointments in physiology and biophysics, and in medicine. He was to be dean for the next 12 years, in a period that saw some of the most challenging and significant developments in the school.

"We were in the midst of change," he said, recalling the situation when he took office:

> On the one hand, it was near the beginning of Health Manpower Legislation, so there were a number of federal initiatives to increase the class size (ultimately ending in capitation legislation), and on the other hand we had just begun to see a bunch of serious cutbacks in our support at NIH.

The challenge was to respond to primary care needs in the Northwest while maintaining the school's record in research.

Shortly before he became dean, the school had voted to develop a strong family practice training program. To head it, Van Citters hired a young physician from Sitka, Alaska, Dr Theodore J. Phillips. With his "remarkably good instincts," Dr Van Citters said, Dr Phillips built the school's Department of Family Medicine into one that remains today as a model for other programs across the country.

Dr Phillips is now the school's associate dean for academic affairs. He recently said,

> When I came to the UW a number of medical schools were beginning to focus on the education of the generalist, but there was a notion that this training had to be separate from a scientific center. This seemed wrong to me. I feel the two should go hand in hand. Contact with medical science is appropriate for the family physician.
>
> The unique thing about the School of Medicine is that it does these two things so well together. It has created a solid reputation as a research intensive, highly scientific medical center. At the same time, it has developed programs relating scientific expertise to the needs of the region and has an equally prominent reputation for training general physicians.

The WAMI Program

The desire to create a new academic department of family medicine was accompanied by a concurrent effort to meet the medical training needs of Alaska, Montana and Idaho. None of these states have a medical school, but the costs of constructing medical schools in these states was prohibitive. The solution to both these problems came during Van Citters' deanship and was the genesis of the widely recognized WAMI Program.

Under the program, which quickly became a national

Figure 4.—A student in the WAMI Program of Regionalized Medical Education gives a chest examination to a Pocatello, Idaho, rancher. One of the goals of the WAMI Program is to train physicians for rural practice. Physicians at 17 community clinical units in the four-state WAMI region supervise medical students.

model, students from the WAMI states (Washington, Montana, Alaska and Idaho) take their first year (basic science) studies at a university in their home state. All students come to Seattle for their second year classes. Upper level students, regardless of whether or not they entered medical school through the WAMI Program, are eligible to obtain clinical experience at 17 sites in communities throughout the WAMI states. Physicians at the community clinical units who hold faculty appointments at the School of Medicine give students and residents an opportunity to see medicine as it is practiced away from a large metropolitan center. The decentralized medical education program takes place in a geographical area that occupies one fourth of the land mass of the United States and spans four time zones (see Figure 4).

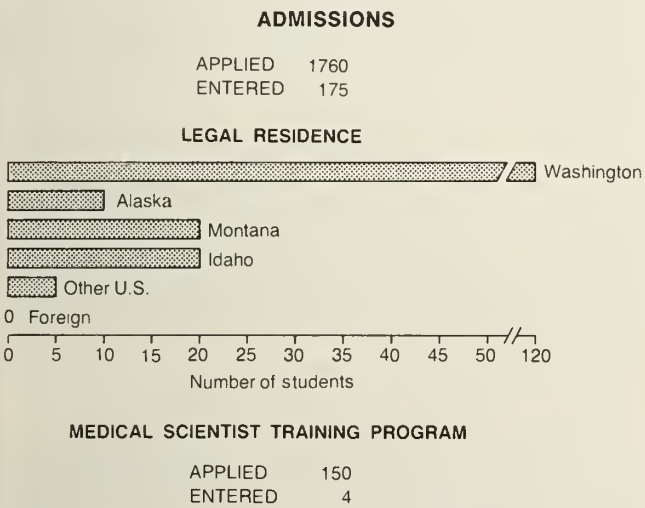

Figure 5.—Profile of entering class at the University of Washington School of Medicine.

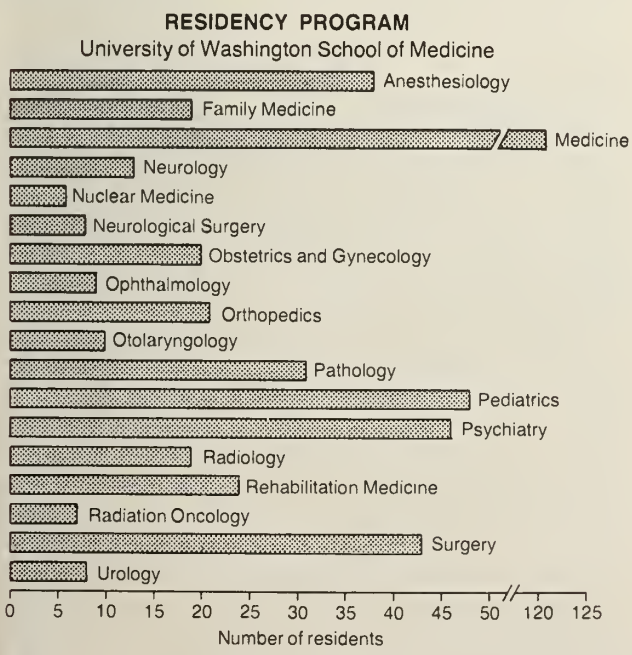

Figure 6.—The residency program at the University of Washington School of Medicine has 491 trainees in 16 programs.

The WAMI Program got going at a social hour during a meeting of the Washington State Medical Association, Dr Van Citters recalled:

> Gus Swanson, Tom Morgan [the school's former assistant dean for curriculum], Pres Bratrude [a family doctor from the town of Omak in eastern Washington], Jack Lein [associate dean for Continuing Medical Education] and I were discussing the problem and as an immediate action kind of thing Pres said, "Send me those students, I'll teach them." Before the evening was through, the term community clinical unit had been coined and the general plan for the WAMI Program had evolved.

Dr Van Citters asked Dr Swanson to write a position paper on the discussion and that became the basis for a successful presentation to the Commonwealth Fund for the creation of a regional medical program to serve, in addition to Washington, the states of Alaska, Montana and Idaho.

With the seed money provided by the Commonwealth Fund, Dr Van Citters and Dr M. Roy Schwarz, whom he chose to direct the WAMI Program, went after federal funding to further establish the program. Today, WAMI is entirely supported by the participating states.

Although it is highly unusual to have states appropriate funds to a school in another state as happens with WAMI, the dean was confident it would happen. "It's an enormous bargain," he said. "Any legislator who would take the time to think it through would look on it as a good investment. Both houses of our own legislature approved WAMI without a single dissenting vote."

Teaching, Medical Care and Research

Today the School of Medicine serves a class of 175 students, 50 of whom are enrolled through the WAMI program (Figure 5) and 491 trainees in 16 residency programs (Figure 6). In addition, the school provides continuing medical education to physicians in the Pacific Northwest and Alaska.

During Dr Van Citters' deanship the school's two teaching hospitals played increasingly prominent roles as local and regional referral centers. At Harborview, new services were created such as the Burn Center, Trauma Center, Primary Care Center, Epilepsy Center and several others. University Hospital developed special programs such as the Spinal Cord Injury Center, organ transplantation, cardiac surgery, radiation oncology and a regional high risk obstetrics and newborn intensive care center. The affiliations with Seattle area hospitals became stronger under Dean Van Citters with new agreements with Children's Orthopedic Hospital and Medical Center and Group Health Cooperative of Puget Sound.

Under Dr Van Citters' deanship the number of multidisciplinary centers within the School of Medicine grew to twenty. He considers the school's tradition of collaboration among disciplines one of its major strengths.

The School of Medicine also continued its strong research orientation under Dr Van Citters; in fact, it ranks consistently among the top four medical schools

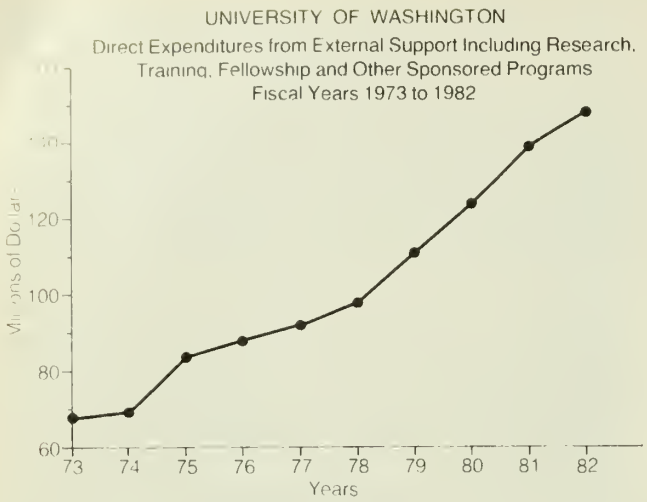

Figure 7.—For the past ten years, the University of Washington has ranked among the top four (including two years as first) universities in the amount of federal grants and contracts awarded. Roughly a third of the support goes to the School of Medicine. The funds are awarded in response to faculty-initiated, University-approved, proposals.

in this country in the amount of federal research dollars received each year (Figure 7). He is worried, however, about the decline in training grants.

"I remember when I was a faculty member in physiology there were six training programs in the department, and we were attracting absolutely first-class bright young people from all over," he recalled. It was much the same in many other departments. "We don't have all those positions to offer now. Those young people are the future of our institution. That's our tomorrow."

In 1981 Dr Van Citters announced that he was resigning to return to research. He recently was awarded two major grants to develop and implement a curriculum in preventive cardiology for medical students and residents.

In spite of the challenge of "maintaining our position," Dr Van Citters thinks the school is stronger today than when he became dean and will remain so. One real challenge facing the school now, he said, is the changing attitudes of the public toward the medical profession.

John D. Chase, MD—Fifth Dean

Succeeding Dr Van Citters, first on an acting, then permanent basis, was Dr John D. Chase. Recruited by Dr Van Citters as associate dean for clinical affairs, Dr Chase was the chief medical director for the Veterans Administration in Washington, DC, from 1974 to 1978. His career in the Veterans Administration covered 26 years, beginning with his appointment as a staff physician at the Veterans Administration Hospital in Vancouver, Washington, and ending with his four-year term as one of the nation's highest-ranked medical officials.

He found the School of Medicine a "terribly exciting environment with great opportunities to make a contribution because of its excellent nature, its diverse programs, and its accomplished faculty." Further, Dr Chase said, the school had "sufficient problems that I felt I might be able to make a contribution." One of the major problems he faced as associate dean was a threatened strike by the housestaff. Through exhaustive, and exhausting, discussions the school and housestaff were able to resolve their differences. "The end result was constructive," Dr Chase said. "We achieved both a better understanding with the housestaff as an organization and a better clarification of what our principles and rules were."

Another problem Dr Chase confronted was a large number of vacant department chairmanships. Most of them resulted from the mandatory retirement of the founding chairmen. The stringent budgetary situation he inherited impeded Dr Chase's attempts to recruit chairmen, as did his six months as acting dean, when he felt he could not move ahead with full vigor in recruiting.

When he was appointed permanent dean in January 1982, Dr Chase intensified the process. That May, he suffered a mild, but worrisome, heart attack. He has noted,

> Within three days I became personally convinced that the school didn't need a 62-year-old dean with a fresh coronary to deal with all the problems of the immediate future. Because my tenure had been so short, I felt that the cost of finding a new dean would not be too great.

Theodore Phillips, MD—Acting Dean

So a new search for a dean was conducted in the summer of 1982. In the interim, Dr Theodore Phillips served as acting dean. Dr Phillips has since returned to his post as associate dean for academic affairs at the school. One of the responsibilities of his office is overseeing the curriculum.

Curriculum

"The school has a dynamic, responsive curriculum," Dr Phillips said, "it is constantly under change and revision. The committee Aagaard appointed to look at the school's educational programs filed its report in 1965," he said. "They saw ahead to the present and predicted the need for comprehensive care of patients and an increased need for an integrated approach in medical education."

A new curriculum was established in 1968. Some elements of this curriculum have done so well that they not only remain in effect, but also serve as models for other schools. Other elements have been abolished. What remains includes an organ systems approach to teaching, interdisciplinary instruction in basic and clinical sciences and an early introduction to clinical medicine. Also remaining from the 1968 revision is the notion that students should have a certain amount of elective time. While this is still a goal of the school, the required course load makes it difficult to maintain, Dr Phillips said.

A change in faculty and student attitudes led to an-

other curriculum change in 1981. One aspect abandoned from the 1968 revision was the early differentiation of students according to career interest. Back in the mid-1960s, faculty felt students should be asked to decide, as soon as possible, what type of medical practice they wanted to pursue. This belief was manifested by permitting students to choose a pathway: family physician, medical specialist, behavioral specialist or medical scientist. Since the 1981 revision, all students are now required to take the same basic curriculum and required clinical clerkships in eight disciplines. The current curriculum produces graduates with a common core of knowledge ready to enter any of the medical specialties.

The new curriculum also requires students to complete an independent study in the medical sciences that involves them directly in scientific inquiry, Dr Phillips said. The planners of the new requirement hope it will enable students to critically evaluate new research and prepare them to continue their self-education after they leave school.

David C. Dale, MD—Present Dean

Acting Dean Phillips was succeeded by Dr David C. Dale, whom Dean Chase had appointed as his associate dean for clinical affairs. Dr Dale is a *cum laude* graduate of Harvard Medical School and has an impressive record as a teacher and clinical researcher. Like several past and present School of Medicine administrators, Dr Dale first came to Seattle as a chief medical resident.

In describing the school he was chosen to head, Dr Dale defined its distinguishing qualities: the breadth of its research and clinical programs, its regional character and the strong emphasis on training for primary care.

A Four-State Region

Being at the only medical school for a four-state region has "lifted the faculty's horizon in thinking about the organization of medical education and the delivery of medical service," he said. Far from ensconcing themselves in an ivory tower of academic medicine, many of the school's faculty members work closely with doctors in the community. The faculty consults with community doctors on patient problems through MEDCON, a toll-free telephone line that connects physicians in the Pacific Northwest and Alaska with the expertise of the School of Medicine physicians any hour of the day or night. A regional poison control center, blood bank, air transport service, library and a host of other services reflect this regional character as well. The faculty also provides continuing education to community physicians through courses in Seattle and visits throughout the region. In turn, hundreds of community physicians, from Nome, Alaska, to Glasgow, Montana, assist with the clinical training of medical students.

"We have a formal commitment to be interested in members of our profession and the quality of medical services across the Northwest," Dr Dale said.

Organizing a regional medical education program has brought us into close contact with local doctors, and helped us to establish collegial relationships. This has enabled our students to gain firsthand knowledge of what the medical profession is about from both our full-time faculty and from those who practice medicine on a daily basis.

"We want to train doctors to serve the people of this whole region," Dr Dale said, "that's why the school has tried hard to assure a good balance of programs in undergraduate and graduate medical education, particularly among residency programs." The school does this, Dale explained, by cooperating with many clinics and hospitals to match support for graduate training with the need for generalists and specialists in this region.

In facing these and other challenges, Dr Dale said there are benefits of being at a young school.

"It's nice to have the founders around," the school's sixth dean said. "You can talk with them about almost any issue and get the full history. The faculty is a devoted and loyal group whose members are very proud of the school because they had a personal hand in its making."

Dr Dale outlined some current goals and directions for the school as follows:

The school is going through a transition as a number of the faculty who made the school have recently retired. We have recruited successors with equal energy and vision. We want a new level of greatness for the school.

In biomedical research we have more questions than ever. We have become a foremost center for biomedical investigation. We as a faculty want to remain at the forefront of new discoveries.

The school is already a leader in innovative methods in organizing medical education. We hope to continue in that role by refining our regional education program and providing new impetus for continuing medical education. We want to expand the use of computers in medical education. We would also like to develop a strong program in international medical education.

On the clinical side, our faculty staff a group of Seattle hospitals. I anticipate that our relationships with these hospitals will grow and become stronger. Our place in providing care will continue to grow because of the abilities of our faculty.

Commentary

Commentary From Santa Fe: Revitalizing County Medical Society Meetings – A Proposed Reform of the Rules

JONATHAN M. MANN, MD, MPH, *Santa Fe, New Mexico*

As a former president of a county medical society, I recognize the need for rules to guide our organizations' sometimes turbulent debate. However, I am also convinced that we must reform the parliamentary framework under which we currently labor: *Robert's Rules of Order.*

Robert's Rules of Order is a manual of procedure as well as a metaphor for propriety in the conduct of official meetings. For this reason, our county medical society, like thousands of other organizations, boards, commissions, academies and societies, affirms in its bylaws that *Robert's Rules* shall govern its deliberations.

Henry M. Robert (1837-1923) sought to standardize the conduct of the meetings of "ordinary societies" and originally hoped to summarize the necessary rules in a 16-page pamphlet.[1] Good intent notwithstanding, the first edition (1876) contained 176 pages and the third (1893) grew to 218 pages. The 1915 *Robert's Rules of Order, Revised* contained 75% more material than previous editions.[1] Finally, the rules were most recently updated in 1970, in a 594-page book called *Robert's Rules of Order, Newly Revised.* Thus, the evolution of *Robert's Rules* has paralleled our national history. The 19th century desire for national unification and standardization (Manifest Destiny) was reflected in Robert's desire to ensure that "civic-minded people . . . (could) belong to several organizations or move to new localities without constantly encountering different parliamentary rules."[2] Subsequently, the Rules expanded rapidly in an effort to handle all possible situations that might arise (like the proliferation of government programs and regulations in the 20th century).

Rules of procedure are intended to "subserve the will of the assembly . . . to facilitate . . . the expression of their deliberate sense."[2] Unfortunately, *Robert's Rules* actually restrains and obstructs the will of our society. Several of our difficulties with *Robert's Rules* appear in the following typical scenario of a county medical society meeting. First, as people try to operate within an imperfectly understood parliamentary structure, they start talking (and thinking) in a stilted and awkward manner, like a speaker in an unfamiliar dialect. As a result, the debate becomes congested and constrained. Second, the local "parliamentarians," having actually been taught the Rules at one time, run rampant. Whether to assure parliamentary purity or simply to get attention, they (and every group has at least one) loudly insist on points of order and personal privilege, demand that the proper order of precedence of motions be observed and generally disrupt the flow of discussion about an issue with strictly procedural concerns. Next, inevitably, a rules fight breaks out among a small group, while the majority of society members are at first bemused and then repelled by the "triviality" and the apparently senseless turn which the discussion has taken. Finally, as the bulk of the membership becomes alienated from the meeting, avowals never to waste one's time again by attending another such meeting are heard and, by extension, disrespect spreads to the organization itself. In sum, while *Robert's Rules* may work well for experienced parliamentarians, and may even be necessary for very large groups, its use seems to paralyze and may actually harm societies composed of well-intentioned members who, despite their professional qualifications, are rank amateurs in parliamentary procedure.

What is to be done? The root causes of this regrettable situation are general ignorance of the Rules (even among the otherwise well educated) and their

(Mann JM: Commentary from Santa Fe: Revitalizing county medical society meetings—A proposed reform of the rules [Commentary]. West J Med 1984 May; 140:812-813)

Dr Mann has served as president of the Santa Fe County Medical Society and State Epidemiologist, State of New Mexico Health and Environment Department, Santa Fe. He now is on assignment for the Centers for Disease Control.

Reprints not available.

1. Motions are of two types: substantive and procedural.
2. Speakers must be recognized by the chairperson before speaking.
3. Once a substantive motion is made, the motion proceeds through a clearly defined sequence:
   a. *Preliminary Discussion:* Open discussion is designed to clarify the meaning and intent of the motion. During this period, the mover may modify or withdraw the motion.
   b. *Statement of the Motion and Initial Debate:* The chairperson clearly states the motion to ensure clarity. Then, the chairperson invites discussion: first from those speaking in favor, then from those speaking against the motion.
   c. *Call for Amendments:* Each proposed amendment is stated, discussed and voted upon in turn.
   d. *Call for Final Debate:* The motion is restated (including all amendments) and final speakers for and against the final motion are invited.
   e. *Final Restatement of the Motion and Voting:* self-explanatory.
4. *Procedural Motions and Miscellaneous Issues:*
   a. Procedural questions may be raised at any time.
   b. A motion to put aside further consideration of the matter, to refer the matter to a committee or to limit or stop debate can be made. Such requests are immediately voted upon and require a two-thirds vote.
   c. When a procedural question, or a problem not directly covered in these rules arises, or when a deviation from the rules is desired, the concern should be brought to the chairperson, who rules on the issue. If this ruling is not acceptable to two or more members, a vote on the chairperson's ruling is immediately held.
   d. Unless otherwise noted, all motions require a simple majority for passage.
   e. Voting can be by voice vote or show of hands; show of hands can be requested if a voice vote is contested by two or more members.

Figure 1.—Proposed Rules of Order

complexity. Conscious of my parliamentary responsibility towards the county medical society, I purchased a copy of *Robert's Rules.* After several concentrated hours, I acquired a novice's grasp of the approximately 200 most common questions relating to motions and a sense of the overall operation of the Rules. With practice, I believe I could eventually fulfill Robert's charge to the chairperson, smoothly handling motions to commit, to postpone, to amend and to call for the previous question in their proper order of precedence, allowing debate and amendments to each motion when appropriate. However, educating county society members to functional literacy in *Robert's Rules* would be time-consuming, would be unacceptable to many members and may actually be unnecessary.

I would like to propose a reform in the rules guiding the conduct of our "ordinary societies." Each society would examine its bylaws for the chapter entitled "rules of order." This chapter currently expresses blind fealty to *Robert's Rules,* especially since many bylaws are simply copied from earlier models. In place of *Robert's Rules,* the society would specify its own set of guiding principles and rules, whose goal is to ensure open and fair discussion of issues, thereby facilitating the organization's expression of its "deliberate sense." Such reform is consistent with recent national trends favoring local autonomy and fostering greater acceptance of individual and group differences. The virtues of standardization appear less attractive in the 1980s than a century ago.

As an example of this approach to rule-making, a set of simple rules to guide group deliberation is presented in Figure 1.

Can such simplified rules permit orderly consideration of society business, while avoiding the tyranny of either the individual member or the majority? I believe so, especially for small and medium-sized organizations that meet occasionally. The risks of such an experiment in self-governance are few; if a success, substantive discussion may be dramatically enhanced in the county medical and other societies now hobbled by *Robert's Rules.*

A final suggestion—select your chairperson carefully, for discretion in the conduct of your society's meetings will be needed in direct proportion to the brevity and flexibility of your rules. As Robert himself recognized, "No rules will take the place of tact and common sense on the part of the chairman."[2]

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Information

Long-term Results of Extracranial to Intracranial Bypass for Ischemic Vascular Disease

STEVEN L. GIANNOTTA, MD
Los Angeles

MORE THAN A DECADE has passed since the first cases of extracranial to intracranial bypass in humans were reported. Since then improvement in microsurgical techniques and instruments has allowed for an array of microvascular procedures for establishing collateral flow to the brain in cases of ischemic disease. The most common of these is the superficial temporal artery to middle cerebral artery bypass. Other procedures for improving flow in the basilar circulation are being done with increasing frequency. These include occipital artery to posterior inferior cerebellar artery bypass, superficial temporal artery to superior cerebellar artery bypass and intracranial vertebral endarterectomy. Increasing experience with the surgical treatment of ischemic cerebral vascular disease should provide valuable information regarding the management of stroke and its prevention. Now that thousands of superficial temporal artery to middle cerebral artery bypasses have been done, it is important to look at current concepts as well as long-term results.

Indications for this bypass procedure continue to be ischemic lesions in the carotid circulation inaccessible to conventional extracranial vascular techniques, such as endarterectomy. The most common angiographic indication is internal carotid artery occlusion, but a large number of patients with intracranial carotid artery stenosis and middle cerebral artery stenosis and occlusion are felt to be suitable candidates.

Clinical indications include transient ischemic attacks and the presence of a reversible ischemic neurologic deficit. Certain selected patients with completed stroke, especially those with continued ischemic symptoms, are also candidates for the procedure.

Patency rates in well-selected patients continue to be more than 90%. Morbidity and mortality figures are highly acceptable and are comparable to the lowest rates associated with carotid endarterectomy. Permanent neurologic morbidity related to the operation averages 3% to 4%. Patients with a functioning extracranial-intracranial bypass have a number of the following benefits: improvement in electroencephalographic findings, increase in cerebral blood flow and cerebral metabolic rate, reduction in transient ischemic events, improvement in cerebral vasomotor activity and reversal of neurologic deficits.

Despite these well-documented salutary effects of surgically constructed collateral circulation to the brain, questions relating to long-term clinical benefits remain to be answered. Chater has recently cataloged his observations of 400 cases of superficial temporal artery to middle cerebral artery bypass. The average follow-up time was 43 months and the longest was more than ten years.[1] Overall there was a 2.5% mortality rate and a 2.2% permanent neurologic morbidity rate. More than half of the follow-up mortality in those patients was cardiac related. In patients with a functioning bypass there was a 0.9% per year stroke rate on the side of the bypass. Yonekura and co-workers[2] made similar observations in 107 cases followed for more than 25 months: 82% of their patients showed lessening of transient ischemic attacks and 70% eventually recovered from neurologic deficits. They found a 1.5% stroke rate per year in patients who had a functioning bypass. Thus there seems to be some long-term protective effect of a functioning bypass in selected patients.

Unfortunately, the above-mentioned studies suffer from the lack of a simultaneously treated control group. In hopes of answering continued questions related to long-term clinical benefits, an international multicenter randomized study initiated in 1977 should conclude and be available for scrutiny within the next year. The study, funded by the National Institute of Neurological and Communication Disorders and Stroke (NINCDS) and based in London, Ontario, will compare a group of randomly selected patients who have ischemic symptoms treated either nonsurgically or with a superficial temporal to middle cerebral artery bypass. End points are stroke and death due to stroke and should provide some valuable information regarding the long-term efficacy of this particular surgical procedure.

(Giannotta SL: Long-term results of extracranial to intracranial bypass for ischemic vascular disease [Information]. West J Med 1984 May; 140:814)

From the Department of Neurosurgery, University of Southern California School of Medicine, Los Angeles.

Reprint requests to Steven L. Giannotta, MD, LAC/USC Medical Center, 1200 N State Street, PO Box 239, Los Angeles, CA 90033.

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In Memoriam

California Medical Association

ANTEL, JOHN J., Mountain View. Died January 30, 1984, of cancer, aged 62. Graduate of the University of Chicago, The School of Medicine, 1945. Licensed in California in 1954. Dr Antel was an associate member of the Santa Clara County Medical Society.

BASSETT, CLYDE G., Escondido. Died October 9, 1983, aged 68. Graduate of Northwestern University Medical School, Chicago, 1942. Licensed in California in 1947. Dr Bassett was a member of the San Diego County Medical Society.

BERKE, MEYER, Lakewood. Died July 5, 1983, aged 69. Graduate of Ohio State University College of Medicine, Columbus, 1942. Licensed in California in 1943. Dr Berke was a member of the Los Angeles County Medical Association.

CAMPBELL, DOUGLAS GORDON, San Francisco. Died October 16, 1983, in San Francisco of cancer, aged 81. Graduate of the University of Toronto Faculty of Medicine, 1925. Licensed in California in 1940. Dr Campbell was a member of the San Francisco Medical Society.

EINERT, AMY CHRISTINE, Oakland. Died December 21, 1983, aged 81. Graduate of Columbia University College of Physicians and Surgeons, New York, 1928. Licensed in California in 1947. Dr Einert was a retired member of the Alameda-Contra Costa Medical Association.

GELLER, PHILIP S., Redwood City. Died January 29, 1984, in Napa of myocardial infarct, aged 76. Graduate of Tufts College Medical School, Boston, 1931. Licensed in California in 1944. Dr Geller was a retired member of the San Mateo County Medical Society.

GOLD, ERNEST M., Davis. Died September 22, 1983, in Woodland of heart disease, aged 56. Graduate of Wayne University College of Medicine, Detroit, 1954. Licensed in California in 1955. Dr Gold was a member of the Yolo County Medical Society.

HUGHES, CLARA L., Patton. Died December 22, 1983, of heart disease, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr Hughes was a retired member of the San Bernardino County Medical Society.

KAHLSTROM, CARL E., Long Beach. Died June 30, 1983, aged 76. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Dr Kahlstrom was an associate member of the Los Angeles County Medical Association.

LINDSEY, JAMES O., Santa Monica. Died June 14, 1983, aged 83. Graduate of the University of Southern California School of Medicine, Los Angeles, 1933. Licensed in California in 1933. Dr Lindsey was a member of the Los Angeles County Medical Association.

MACKEY, JOHN F., JR, Santa Ana. Died April 9, 1983, aged 72. Graduate of St Louis University School of Medicine, 1941. Licensed in California in 1957. Dr Mackey was a member of the Orange County Medical Association.

MILLS, LEROY K., Carmichael. Died August 20, 1983, aged 64. Graduate of Northwestern University Medical School, Chicago, 1949. Licensed in California in 1955. Dr Mills was a member of the Sacramento-El Dorado Medical Society.

RANDOLPH, HOMER E., Los Angeles. Died September 7, 1983, in Los Angeles of myocardial infarct, aged 66. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1945. Licensed in California in 1945. MD degree from California College of Medicine, 1962. Dr Randolph was a member of the Los Angeles County Medical Association.

SAMILSON, ROBERT L., San Francisco. Died March 10, 1984, in Tiburon of myocardial infarct, aged 60. Graduate of New York Medical College, New York City, 1950. Licensed in California in 1954. Dr Samilson was a member of the San Francisco Medical Society.

TAYLOR, LLOYD W., San Francisco. Died August 15, 1983, aged 67. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1941. Licensed in California in 1960. Dr Taylor was a member of the San Francisco Medical Society.

Twigg, Edward J., Palm Desert. Died August 18, 1983, aged 67. Graduate of Tufts College Medical School, Boston, 1943. Licensed in California in 1950. Dr Twigg was a retired member of the Alameda-Contra Costa Medical Association.

WASSERMAN, NATHAN, Palo Alto. Died March 4, 1984, in Palo Alto, aged 72. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Dr Wasserman was a retired member of the Santa Clara County Medical Society.

New Mexico Medical Society

ALKIRE, LEONARD E., Espanola. Died in January 1984 in Espanola, aged 55. Graduate of the University of Nebraska College of Medicine, Omaha, 1953. Licensed in New Mexico in 1981. Dr Alkire was a member of the Rio Arriba County Medical Society.

WESTEN, WILLIAM C., Santa Fe. Died February 24, 1984, in Santa Fe, aged 68. Graduate of Northwestern University Medical School, Chicago, 1941. Licensed in New Mexico in 1950. Dr Westen was a member of the Santa Fe County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

SKELETAL MUSCLE PATHOLOGY—Edited by Frank L. Mastaglia, MD-(WA), FRACP, FRCP, Associate Professor of Neurology, University of Western Australia, and Consultant Neurologist, Queen Elizabeth II Medical Center, Perth; and Sir John Walton, TD, MD, DSc, FRCP, Professor of Neurology, University of Newcastle upon Tyne, and Consultant Neurologist, Newcastle Area Hospitals, England. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 630 pages, $95.00.

This excellent new book provides a timely addition in the area of disorders of voluntary muscle. For a number of years there have been excellent monographs primarily devoted to the clinical aspects of muscle disorders. New editions of these clinical monographs have been completed at frequent enough intervals to keep up with this rapidly expanding area of knowledge. Those texts primarily directed towards the pathologic reactions of skeletal muscle have become quite out of date. *Skeletal Muscle Pathology* is up-to-date and includes descriptions of all of the disorders one would anticipate.

The editors have selected a distinguished group of experts to write this book. Each chapter is well written and relatively concise. The discussions of development, pathologic reactions and aging are particularly informative. The only criticism is directed at the editors who allowed certain topics to be covered in more than one chapter. For example, thyrotoxic periodic paralysis was covered in chapters 8 and 12; carnitine palmityl acyl transferase (CPAT) deficiency in chapters 9 and 10. It is to be hoped that these duplications will be eliminated in future editions.

The illustrations have been carefully selected for both quality and quantity. The electronphotomicrographs are of superior quality, demonstrating a sharpness in contrast not seen in most texts.

This book is highly specialized and not intended for general medical practitioners. Neurologists, pathologists and those persons dealing with patients who have diseases of skeletal muscle will find this a useful and authoritative reference book.

DONALD F. FARRELL, MD
Professor of Medicine (Neurology)
University of Washington School of Medicine
Seattle

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ANNUAL REVIEW OF NEUROSCIENCE—VOLUME 6—Edited by W. Maxwell Cowan, Salk Institute for Biological Studies. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA 94306, 1983. 546 pages, $27.00.

The sixth volume of the series *Annual Review of Neuroscience* contains a major change in direction. In contrast to preceding volumes, there are no chapters directed to discussion of purely "clinical" topics. This does not mean that this volume is of no interest to clinical neuroscientists and neurologists. In fact, there are chapters which are sure to pique the curiosity of many clinicians. For instance, the article by Penney and Young on the functional anatomy of basal ganglia disorders, while speculative, is well written and thought-provoking. If not directly applicable to the management of patients with these disorders, this discussion may help the clinical neuroscientist to understand patients with these disorders. Raichle's chapter on position tomography is a brief, precise introduction to this potentially powerful diagnostic and research tool.

As in previous editions, this volume contains articles of great interest to basic neuroscientists. Neurophysiologic topics include the microcircuitry of the cat retina and the visual cortex. Of interest to cell biologists are chapters on dopamine receptor classification and receptor sensitivity modification, on application of molecular biological principles to the study of the nervous system, and on the role of phosphorylation of cellular protein in the regulation of nervous function.

This volume also contains a chapter which should be read by every clinical and basic neuroscientist. This is an essay entitled "Nobel Laureates in Neuroscience, 1904-1981." The authors, Herbert Jasper and Theodore Sourkes, have done a superb job of providing brief yet fascinating accounts of the personalities and work of the most recognized neuroscientists of our century. This essay is readable and well documented. It alone is worth the price of the volume.

GEORGE K. YORK, MD
Clinical Instructor
Department of Neurology
University of California, San Francisco
School of Medicine
San Francisco

* * *

PRACTICAL RHEUMATOLOGY—Edited by Timothy M. Spiegel, MD, Assistant Professor of Medicine, Division of Rheumatology, UCLA School of Medicine, Los Angeles. John Wiley & Sons, Inc., One Wiley Dr., Somerset, NJ 08873, 1983. 375 pages, $29.95.

This book is, to use a popular computer-inspired phrase, "reader friendly." The authors have written and organized a book that will be useful to primary care physicians caring for patients with rheumatic complaints.

The book begins with chapters on the general approach to a patient with joint complaints followed by chapters on the more common rheumatologic syndromes. There is a chapter devoted to the rheumatologic laboratory tests in which the basis and mechanics are discussed and, important to primary care physicians, what their rational use is. Recent developments in therapy are included along with helpful advice on patient education and ancillary measures to improve patients' functional capacities. The sometimes confusing topic of vasculitis is presented in a straightforward manner.

Adequate data are presented in the text with interpretation as to their practical value. The written text is well complemented by clear and concise figures and tables. In a few chapters, however, the staccato style detracts from the informational content.

My criticisms are relatively few. In discussing symmetric polyarthritis, a negative example was used that, in fact, fulfills the first two New York criteria for rheumatoid arthritis. There is a misquote of the minor criteria for the diagnosis of systemic sclerosis in the text but the accompanying table is accurate. Occasional therapies are discussed that express a regional bias not balanced by a discussion of the controversies of such treatment. While this may be acceptable for uncomplicated, common rheumatologic problems, I feel it does a disservice to the physician-reader who is faced with more serious manifestations.

Generally speaking, this book accomplishes what it sets out to do. It should prove useful to primary care physicians as long as its limitations are appreciated.

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Instructor in Medicine
University of California, Davis
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(Continued from Page 728)

September 19-23—**Annual Scientific Program and Postgraduate Course of the Pacific Coast Fertility Society** at Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

September 20-23—**34th Annual Obesity and Associated Conditions Symposium.** American Society of Bariatric Physicians at MGM Grand Hotel, Reno. Thursday-Sunday. 17 hrs. Contact: Randall B. Lee, Exec. Dir., 4730 E. Caley Ave., Ste. 210, Englewood, CO 80111. (303) 779-4833.

October 1—**Nutrition Symposium.** UCSF at Yosemite. Monday.

October 8-19—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

October 11-14—**A California Conference in Applied Clinical Geriatics.** UCD at Napa Valley. Thursday-Sunday.

October 12-13—**Skin From A to Z.** UCSF. Friday-Saturday.

October 12-13—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $200.

October 29-November 1—**Interstate Postgraduate Medical Association Meeting** at Las Vegas. Monday-Thursday. Contact: H. B. Maroney, Exec. Dir., PO Box 1109, Madison, WI 53701. (608) 257-6781.

ALASKA

June 8-12—**Alaska State Medical Association Annual Meeting.** Valdez Convention Center. Friday-Tuesday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 277-6891.

June 9-16—**Advances in Pulmonary Medicine: An EPIC Medical Expedition.** American Institute of Primary Care Medicine and University of Arizona College of Medicine at Katmai National Park. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

(Continued on Page 821)

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Active duodenal ulcer healing through effective acid control

- ☐ Just one tablet every twelve hours effectively controls acid secretion day and night—b.i.d. dosing*
- ☐ Effective duodenal ulcer healing in 2**-4 weeks.
- ☐ No interaction with warfarin, theophylline or diazepam.
- ☐ Headache has been reported in about 3% of patients.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers. Despite some similarities in pharmacokinetics, after 10-12 hours Zantac 150 mg still provides a 40% reduction in acid output compared to 1% for cimetidine 300 mg, thus providing a rationale for b.i.d. dosing.

**37% of patients can be expected to show complete healing at the end of two weeks; if healing is confirmed, treatment can be discontinued.

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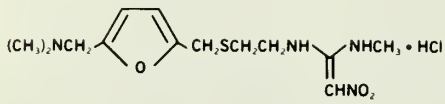
Please see complete prescribing information on the following page.

The first advance in H_2-antagonist therapy

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTION: The active ingredient in ZANTAC® Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure:



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLOGY: ZANTAC® (ranitidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. **Effects on acid secretion**:
ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC® on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. **Effects on other gastrointestinal secretions:**
Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.
Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. **Other pharmacological actions:**
a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. **Pharmacokinetics:**
ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:
Duodenal Ulcer
In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC®-treated patients as shown below

	ZANTAC® +		Placebo +	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid	
	Ulcer Healed	Ulcer Not Healed
ZANTAC®	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIONS AND USAGE:
ZANTAC® (ranitidine hydrochloride) is indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC® (ranitidine hydrochloride).

PRECAUTIONS:
General
1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests
False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction
Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility
There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. Coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy
Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC® (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in children have not been established.

Use in Elderly Patients
Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS
Headache has been found to be more frequent in ZANTAC®-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC® in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:
Duodenal Ulcer
The current recommended adult oral dosage of ZANTAC® for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED
ZANTAC® Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

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(Continued from Page 818)

IDAHO

June 23-27—**Ethics at the Edges of Life.** University of Washington School of Medicine at Elkhorn, Sun Valley. Saturday-Wednesday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 7-13—**Updates in Trauma: An EPIC Medical Adventure.** Bicycle Tour through the Rocky Mountains, beginning in Sun Valley. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

July 25-28—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, 407 W. Bannock St., PO Box 2668, Boise 83701.

August 5-11; 12-18—**Computers in Professional Practice: An EPIC Medical Expedition.** Tyrolean Lodge, Sun Valley. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 15-21—**Updates in Pediatrics: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

September 9-14—**Up-to-Date Cardiac Therapy: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. Sunday-Friday. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 18-24—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** Fishing and Chukar hunting adventure on the Main Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.
***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.
Dosage: Individualize for maximum beneficial effect. *Adults.* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
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MONTANA

September 21-22—**American College of Physicians—Regional Meeting.** Heritage Inn, Great Falls. Friday-Saturday. Contact: Warren D. Bowman, Jr, MD, Billings Clinic, Box 2555, Billings 59103.

October 4-6—**Montana Medical Association Annual Meeting.** Sheraton, Billings. Thursday-Saturday. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (500) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 18-19—**Breast Cancer: Current Concepts and Controversies.** Albuquerque. Friday-Saturday. Clarion Four Seasons Hotel. 10 hrs. AMA Cat. I, NM Cat. IV. Contact: Office of CME, UNM School of Medicine, Albuquerque 87141. (505) 277-3942.

May 19—**Neck and Arm Pain.** Taos. Saturday. Holy Cross Hospital. 1 hr. AMA Cat. I, NM Cat. IV. Contact: UNM School of Medicine, Office of CME, PO Box 531, Albuquerque 87131. (505) 277-6611.

May 24-25—**Chronic Pain: Current Status and Future Directions.** Santa Fe. Thursday-Friday. La Fonda Hotel. 10¼ hrs. NM Cat. IV. Contact: Ms Helene Slansky, Coordinator, Santa Fe Neurological Sciences Institute, St. Vincent Hospital, Box 5764, Santa Fe 87501. (505) 983-4744.

June 8-9—**New Mexico Chapter, American College of Surgeons.** Las Cruces. Friday-Saturday. Holiday Inn. Contact: Robert H. Wilbee, MD, 2435 Telshor Blvd., Las Cruces 88001.

June 29-30—**Genetics in Modern Obstetrics—Advances in Prenatal Diagnosis.** Santa Fe. Friday-Saturday. Hilton Inn. 10 hrs. NM Cat. IV. Contact: VIVIGEN, Sterling Puck, MD, 550 St. Michaels Drive, Santa Fe 87501. (505) 988-9744.

July 12-14—**New Mexico Ophthalmological Society Annual Meeting.** Santa Fe. Thursday-Saturday. Hilton Inn. 8½ hrs. NM Cat. IV, AMA Cat. I. Contact: Kim Knowles, MD, 1452 St. Francis Drive, Santa Fe 87501. (505) 982-2509.

July 16-19—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

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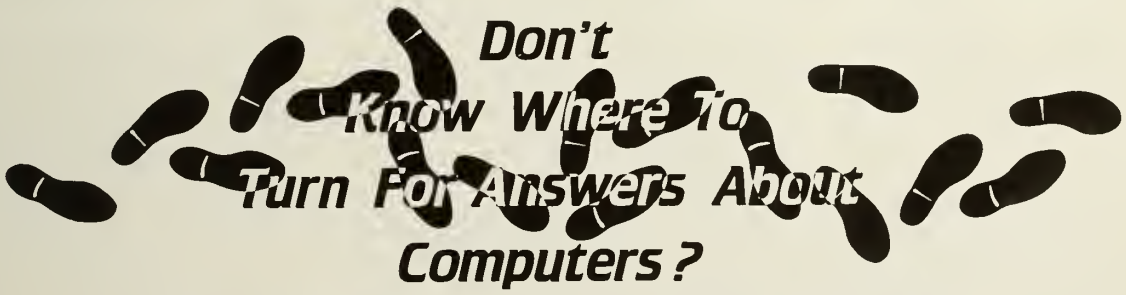
(Continued on Page 829)



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THE WESTERN JOURNAL OF MEDICINE
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GENERAL INTERNIST, Board certified/eligible: Multi-specialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact A. J. Grose, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

BEAUTIFUL WASHINGTON STATE—One General Internist sought to join another Internist in an HMO with 15 well-trained Board-certified Family Practitioners in Spokane, Washington. An unusual opportunity to serve as a full-time in-house consultant in an organization where continuity of care, patient education/preventive medicine, and high quality personal-style care are emphasized. Prefer interest/training in medical Oncology or Geriatrics. Excellent salary and benefits. Spokane is a delightful city containing an exceptionally fine medical community and superb, year-round outdoor recreation. Affiliated with Group Health Cooperative of Puget Sound. For further information contact: Carl Baum, MD, Group Health of Spokane, N. 3919 Maple Street, Spokane, WA 99205; (509) 326-6900.

PEDIATRICIAN—Solo practice in Southeastern New Mexico. Ideal family living in prosperous community serving 85,000. Income guarantee, new office available adjacent to 106-bed JCAH-accredited hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

NEUROSURGEON—Southeastern New Mexico. To establish new practice in growing community serving 85,000. New 106-bed hospital, JCAH-accredited. Has newly operational CAT. Income guarantee. New office available adjacent to hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

ORTHOPEDIC SURGEON—Solo practice in Southwestern New Mexico. Ideal family living in prosperous community serving 85,000. Income guarantee. New office located adjacent to 106-bed, JCAH-accredited hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

IMMEDIATE OPENINGS—Sunny Southern California Immediate Medical Care Center needs experienced physicians with Emergency Medicine or strong Family Practice background. Must have excellent patient empathy and communication skills. Requires well rounded abilities in office based Orthopedics, Minor Surgery, Pediatrics, and Family Medicine. Contact: Kathy Nungester (213) 633-2273 or (213) MED-CARE.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career-oriented emergency physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 234-4795, or send CV to EMP, P.C., P.O. Box 3398, Casper, WY 82602-3398.

SOUTH DAKOTA: Expanding physician-owned emergency group has opening for full-time career-oriented emergency physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD., (307) 234-4795, or send CV to EMP, P.C., P.O. Box 3398, Casper, WY 82602-3398.

ASSOCIATE WANTED. For busy female GP, Canoga Park (LA County). Call (818) 702-9962. Dr Serena Friedman, 22030 Sherman Way, Canoga Park CA 91303.

BOARD CERTIFIED Oncologist, Cardiologist, Internist, Neurosurgeon, Otorhinolaryngologist for Southeastern Washington—Tri-Cities, 150,000 population. Outdoor activities abound. Group or solo opportunities. Contact Vesta Skiens, Kennewick General Hospital (509) 586-6111 (309).

SOUTHERN CALIFORNIA HMO seeking experienced specialists and General Practitioners for health care centers in Los Angeles and Orange Counties. CIGNA Healthplans of California, formerly INA and Ross Loos Healthplans, offers competitive salaries and excellent benefits. Opportunity to join an established, growing and progressive company. CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 N Brand Blvd, Suite 500, Glendale, CA 91203.

INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WANTED FAMILY PRACTITIONER(S). Gateway to the Oregon Caves. 15,000 plus residents in lovely valley. Excellent referral system. 29 miles from hospitals. Enjoy the excitement of a rural family practice and time to spend outdoors. Board of Directors anxious to expand to meet community needs. Now available, one-half fully equipped modern clinic. Room for one or two physicians with excellent expansion potential. Expansion could be emergency type care or convalescent home. Call AC (503) 592-3916 or 592-2224 evenings or weekends.

BOARD CERTIFIED OR ELIGIBLE INTERNIST to become associated with two established physicians in primary care practice in Southern California. Practice incorporated with established pension, continuing education and life insurance programs. Competitive starting compensation with full participation in earnings as ultimate objective. California license required. This opportunity could be of interest to Board certified or eligible Hematologist/Oncologist as an avenue to establish a practice in his specialty. Reply: Medical Practice, P.O. Box 6504, Fullerton, CA 92634-6504.

CAREER EMERGENCY PHYSICIAN. Unique opportunities for selected career emergency physicians to receive highly competitive income, growth and advancement potential, in an educationally oriented environment with academic credibility. Contact Steven J. Davidson, MD, FACEP or David K. Wagner, MD, c/o Institute for Emergency Medicine, 3300 Henry Avenue, Philadelphia, PA 19129 or call (215) 842-6544.

POSITION OPEN: Medical Ophthalmologist wanted in large midwest practice that is affiliated with university training program. Excellent medical skills required. Knowledge of Argon Laser preferable. Opportunity to assist in surgery and learn Yag Laser available. Salary $75,000 plus generous benefits and rapid advancement depending on qualifications. Send résumé to: Box 6379, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

(Continued on Page 830)

ARA services

SPECTRUM EMERGENCY CARE, Inc.

Career emergency medicine positions are available with the nation's largest group in the following states:

California	**Montana**	**S. Dakota**
Colorado	**Nebraska**	**Utah**
Idaho	**Nevada**	**Washington**
Kansas	**N. Dakota**	**Wyoming**

Spectrum provides career emergency physicians with a competitive income; professional liability insurance; and reimbursement of CME tuition, ACEP dues, ACLS and ATLS training. For complete details on positions available in the states listed above contact:

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Spectrum Emergency Care, Inc.
6275 Lehman Drive
Suite C 202
Colorado Springs, CO 80918

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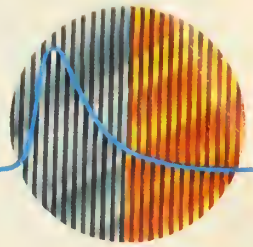
MUTUAL PROTECTION TRUST
Cooperative of American Physicians, Inc.
7080 Hollywood Boulevard, Suite 405 Los Angeles, California 90028
(213) 467-4700

Halcion® 0.25 mg Tablets

triazolam Ⓒ IV

Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion

triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

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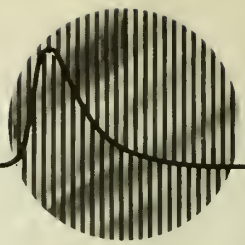
Halcion Tablets
triazolam (IV)



Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

(Continued from Page 823)

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * *

EMERGENCY MEDICINE

June 7-8—**4th Annual Northwest Toxicology Conference.** Portland. Thursday-Friday. Marriott Hotel. Contact: OHSU-CME.

June 13-15—**Oregon Chapter, American Trauma Society.** Portland. Wednesday-Friday. Sheraton-Airport. Contact: OHSU-CME.

November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

(Continued on Page 835)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued from Page 824)

BOARD CERTIFIED GENERAL INTERNIST to join one in growing private practice in Central California. City of 115,000, one and a half hours from San Francisco; Sacramento; five and a half hours from Los Angeles. Excellent opportunity. Contact Barbara Mandell, MD, 1700 McHenry Village Way, Modesto, CA 95350.

MINOR EMERGENCY CLINIC: Full-time physician opening for the Sacramento area. One year contract minimum. Malpractice coverage provided. Dr Kendall Bauer, 815 Mast Ct, Folsom, CA 95630; (916) 933-1449 evenings.

GENERAL PRACTITIONER—to join busy 12 physician office in beautiful Napa Valley. Must be skilled in minor surgery, office orthopedics and capable of inpatient and outpatient care of general medical problems. Contact: Ernest Arras, MD, Permanente Medical Group, 3284 Jefferson Street, Napa, CA 94558; (707) 255-3942.

OBSTETRICIAN & GYNECOLOGIST—needed for expanding HMO in Southern California. Multispecialty group with facilities in Los Angeles and Orange Counties. CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 N Brand Blvd, Suite 500, Glendale, CA 91203.

GENERAL INTERNAL MEDICINE SPECIALIST position open with 37-member multi-specialty group. Excellent practice opportunity; full range of benefits; early shareholder status; all practice costs paid. Prefer recent residency trained physicians. For more information contact: Daniel Small, MD, Medical Director, or David Graham, Asst. Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St, San Luis Obispo, CA 93401.

EVALUATION MEDICINE: Fast growing evaluation practice is establishing a new office in the Bay area. Specialties sought are Board certified: **INTERNIST: Cardiologist, Gastroenterologist, Pulmonary Specialist; ALLERGIST/IMMUNOLOGIST; NEUROSURGEON; PSYCHIATRIST.** This is an excellent opportunity for the practitioner who wishes to supplement his/her income or for the retired or semi-retired practitioner who wishes to work only part-time. This unique practice provides ALL management and support functions while allowing each physician complete flexibility in the scheduling of appointments. Please call or write Mr Gregory Blanchard, Medical Evaluation Specialists, 1127 Wilshire Boulevard, Suite 1209, Los Angeles, CA 90017; or call (213) 977-0540.

FAMILY PHYSICIAN WANTED—Board certified or eligible to join a progressive, primary care based multi-specialty group in Northwest Washington. Close to excellent outdoor recreational opportunities as well as CME. Contact: Shane Spray, Administrator, 1400 E. Kincaid, Mt. Vernon, WA 98273; (206) 428-2524.

CLARKSTON, WA: An excellent opportunity exists for FP's in our "Evergreen Clinic." Located adjacent to a progressive, community-owned hospital, we offer an ideal situation for residency-trained physicians. Flexible and creative programs are available to assist you in creating a solid patient and financial practice in a "banana belt" area of the Pacific Northwest. Contact: Dave Farlowe, Administrator, Tri-State Memorial Hospital, Inc., 1221 Highland Avenue (PO Box 151), Clarkston, WA 99403. (509) 758-5511.

CLINICAL FACULTY, FAMILY PRACTICE—Board certified Family Physician needed to staff FP residency satellite office in a community of 3,500 population located 15 mi. from the primary office in Spokane, Washington. Duties include: full spectrum of patient care (including OB), responsibility for satellite office management, and supervision/teaching of FP residents while working in the satellite. Univ. of Washington clinical faculty appointment. Salary based on experience, excellent fringe benefits. Send inquiries with CV to: Kenneth E. Gudgel, MD, Director, Family Medicine Spokane, South 511 Pine St, Spokane, WA 99202.

FAMILY PRACTICE PHYSICIANS: Rural clinic in S.W. Washington with full support lab. X-ray in office. Full or part-time work available. OB optional. Within 18 mile radius of 3 hospitals with full support services. Submit CV to 503 S. Highway 603, Chehalis, WA 98532.

PHYSICIANS WANTED

FAMILY PRACTICE OPPORTUNITIES in Seattle, Washington. Work as part of a community wide primary health care delivery system serving low and moderate income Seattle residents. Opportunities for up to 8 Family Practice Physicians in the following Seattle Area Community Health Network organizations: Central Seattle Community Health Centers, Neighborhood Health Centers of Seattle, Providence Hospital affiliated Family Practice Center, Pacific Medical Center, Seattle-King County Department of Public Health Clinics. Positions available between July and December 1984. Excellent hospital affiliations available with all positions. Responsibilities include OB, preceptorship of mid-level practitioners, some evening hours, rotating call sschedule. Must be Board eligible in Family Practice. Salary based on experience, excellent fringe benefits. Please send résumé to: Seattle Area Community Health Network, 925 Seneca Street, Seattle, WA 98111. Equal opportunity employer. Women and minorities encouraged to apply.

POSITION AVAILABLE IN GENERAL INTERNAL MEDICINE. Community offers ideal family living in town of 12,000 people, liberal fringe benefits—life insurance, health insurance, 30 days vacation plus 15 days sick leave each year. Complete malpractice insurance coverage provided. An unexcelled opportunity to engage in a challenging medical practice in a rural setting offering unlimited recreational opportunities—hunting, fishing, skiing, plus fresh, clean air in abundance. Contact: P. J. Shannon, Chief, Personnel Service, VA Medical Center, Miles City, MT 59301. Telephone: (406) 232-3060, Ext. 201.

PHYSICIAN FOR PLASMAPHORESIS CENTER, needed to start mid-June. California license req., 4 days per week, no call, low stress position with time for personal reading. North San Francisco Bay City. Contact: Jerome Murphy, MD, c/o Plasma Resources, 332 Tennessee Street, Vallejo, CA 94590. Ph: (707) 644-4119.

FAMILY PRACTITIONER, Board certified or Board eligible needed to join 2 young aggressive Board certified Family Physicians in an already established practice located at the foothills of the Eastern Sierras in rural Northeastern California. Must share on call and do a lot of OB. Salary guaranteed with benefits, vacation and CME stipend. Send CV to: NRHC, 50 North McDow St, Susanville, CA 96130. c/o Paul Holmes, MD (916) 257-7849.

MEDICAL ONCOLOGIST. An ideally located, progressive and family-oriented community offers an excellent professional and living environment for a Board qualified or Board certified Oncologist. Serving this northwest Illinois community is a JCAH approved 250 bed acute care modern hospital with a service area of 54,000. The community offers good primary and secondary schools and a highly rated junior college and is situated near plentiful recreational facilities. Please respond to: Stephen A. Menke, Vice President, Freeport Memorial Hospital, 1045 W Stephenson, Freeport, IL 61032.

NEUROLOGIST. An excellent opportunity awaits a Board certified Neurologist to join a family-oriented, progressive northwest Illinois community. This community offers good primary and secondary schools, a highly rated junior college, plentiful recreation facilities, a modern 250 bed acute care hospital with a service area of 54,000 and a satisfying professional and living environment. Attractive financial arrangements for professional interpretation of EEGs and EMGs. Please respond to: Stephen A. Menke, Vice President, Freeport Memorial Hospital, 1945 W Stephenson, Freeport, IL 61032.

ALBUQUERQUE, NEW MEXICO: 3 positions opening for Emergency Room Physicians beginning June 1, 1984. Training in Surgical, Family Practice, or Internal Medicine acceptable if Board certified or eligible. Rotate between suburban hospital and downtown Level II trauma center. 144 hours per month. Competitive salary plus benefits. Please call/write Jeff Sollins, MD, Medical Emergency Services Presbyterian Hospital c/o ER, 1100 Central E.E., Albuquerque, NM 87102. (505) 841-1125 8-4 p.m.

OREGON—GENERAL INTERNIST sought for multiplespecialty group. Beautiful rural community, 38 miles from Portland. Send CV to Adm., 420 E. 5th St, McMinnville, OR 97128; phone to staff member (503) 472-6161.

PHYSICIANS WANTED

OB/GYN—TULARE COUNTY, CALIFORNIA—Board certified/eligible OB/GYN to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $82,-867-$87,090 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

GENERAL SURGEON. Surgical center office and facilities available. Very reasonable terms with excellent possibilities. Contact administrator, San Fernando Surgical Center, 1056 No. Maclay, San Fernando, CA 91340; Tel: (818) 365-0671.

RESEARCH HEMATOLOGIST. Min. 2 yrs. exp. with related degree to conduct research field of intravascular, clotting, thrombosis and hypercoagulability and its possible cause/effects with human pathologic conditions. Salary $38,000 yr. Send your résumé to Dr Parsa, Physicians Reference Laboratories, 1959 Kingsdale Ave, Redondo Beach, CA 90278.

THE DIVISION OF CARDIOLOGY, Department of Medicine, University of California, San Francisco General Hospital is recruiting for an Assistant Professor of Medicine (In-Residence Series). Candidate will be expected to participate in the teaching and clinical activities of the Division of Cardiology and assume responsibility for the supervision of housestaff, students and fellows in patient care activities, and to carry out a creative academic program. Requirements: Board certified in Internal Medicine; Board certified or eligible in Cardiology with experience in invasive and noninvasive cardiology techniques. Interest in cardiovascular experimental hemodynamics in large animal laboratory is desirable. Applicants should send curriculum vitae, summary of research interests, and names of three references to: Elliot Rapaport, MD, Chief, Cardiology Division, San Francisco General Hospital, Room 5G1, San Francisco, CA 94110. The University of California, San Francisco is an Equal Opportunity/Affirmative Action Employer.

THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, is recruiting an Assistant Professor of Medicine (In-Residence Series) for the Cardiology Division, San Francisco General Hospital. Individual will have primary administrative responsibility for running the Cardiac Outpatient Clinic at SFGH as well as participating in the academic activities of the Cardiology Division including teaching, patient care, clinical research and sufficient time to pursue research activities in his/her area of interest. Applicant should be Board certified in Internal Medicine and Board certified or Board eligible in Cardiology with experience in invasive and noninvasive cardiology techniques. Please address inquiries and CVs to: Elliot Rapaport, MD, Chief, Cardiology Division, Rm. 5G1, San Francisco General Hospital, San Francisco, CA 94110. The University of California is an Equal Opportunity/Affirmative Action employer.

EXTRAORDINARY PRACTICE OPPORTUNITY for Board certified/Board eligible Pediatrician to join very busy practice in a Northern California coastal city. Salarly first year, then partnership if mutually agreeable. Contact: C. Cody, MD, 2800 Harris St, Eureka, CA 95501; (707) 445-8416.

EXPANDING THREE MAN PRACTICE in Vallejo, California, seeks young Board certified Family Practice physician. Complete family practice, must be able to assist in general surgery and do uncomplicated obstetrics. Guaranteed salary, incentive, malpractice insurance, four week vacation, one week CME. Full partnership available after one year. Send curriculum vitae and date available to: Physician Recruitment, PO Box 3297, Fairfield, CA 94533.

GENERAL PRACTITIONERS—Specialists—Full-time positions or Locum Tenens. If you're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

(Continued on Page 836)

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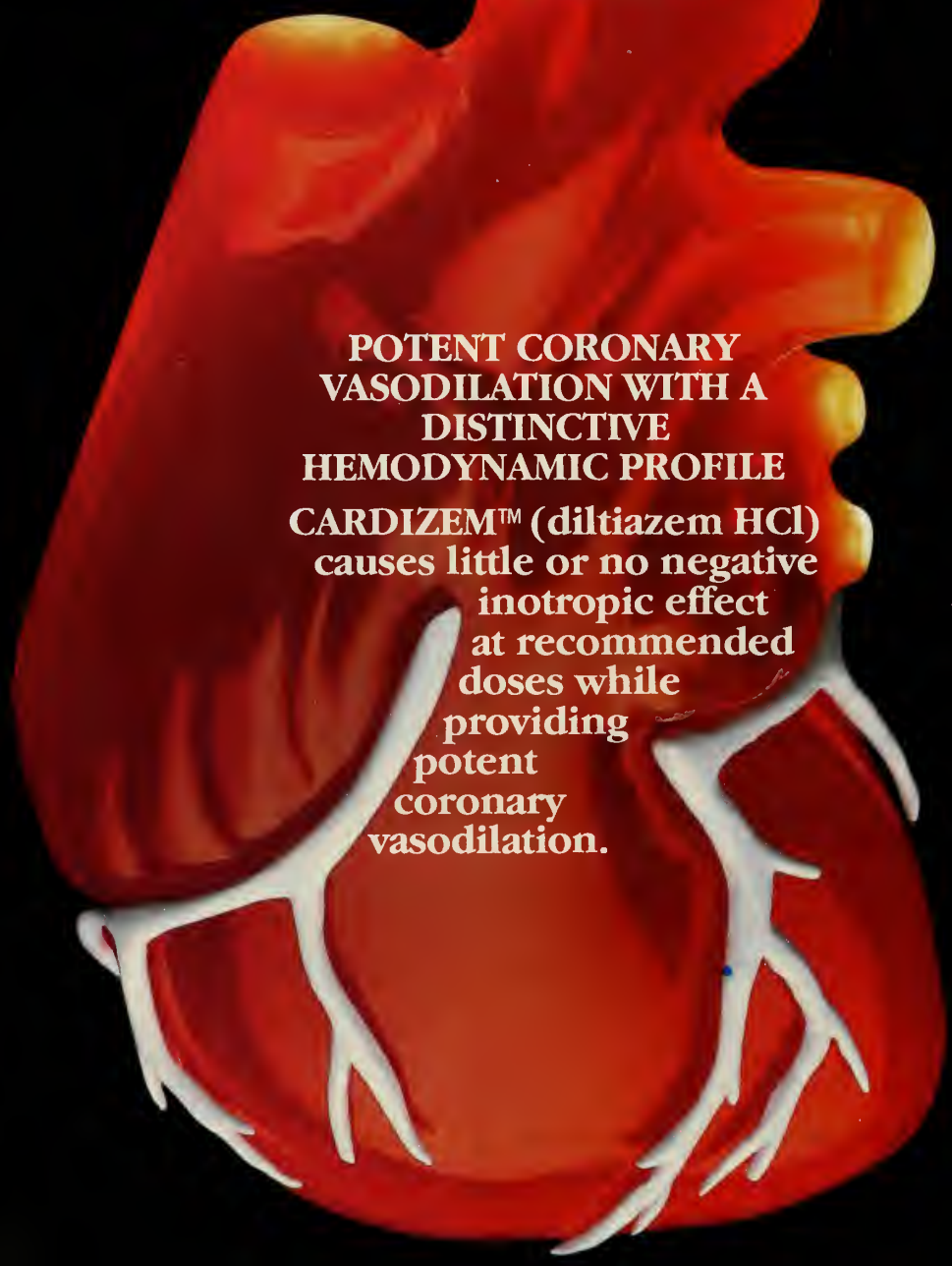
Announcing a major advance in cardiovascular therapy

CARDIZEM™ (diltiazem HCl)

30 mg and 60 mg tablets

CALCIUM CHANNEL BLOCKADE

from
Marion Laboratories



POTENT CORONARY VASODILATION WITH A DISTINCTIVE HEMODYNAMIC PROFILE

CARDIZEM™ (diltiazem HCl) causes little or no negative inotropic effect at recommended doses while providing potent coronary vasodilation.

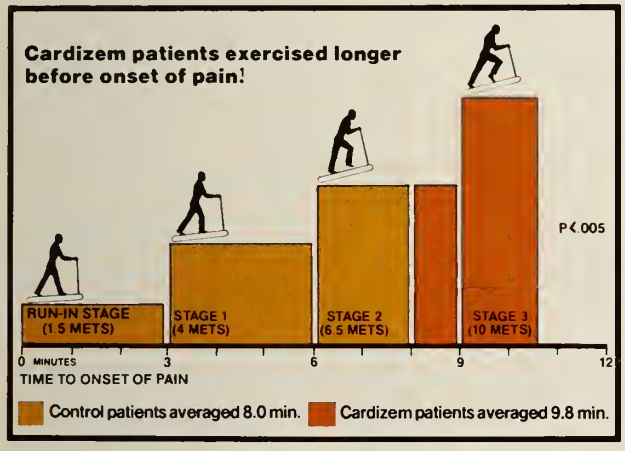
Please see full prescribing information on last page of this ad.

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY* WITH A LOW INCIDENCE OF SIDE EFFECTS

Calcium channel blockade with CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

CARDIZEM™ (diltiazem HCl) ALLOWS PATIENTS TO SIGNIFICANTLY PROLONG EXERCISE TOLERANCE, EVEN IN DEMANDING BRUCE PROTOCOL EXERCISE TESTS[1] (n = 15)†



This study is of special significance because patients not only exercised longer but *to the next higher stage* in the Bruce protocol.

A Bruce protocol with a run-in stage was used for all tests. Each stage lasts three minutes.

In other studies, Cardizem produced 41% to 68% reduction of Prinzmetal's variant angina attacks.[2]

†This study is a report from one center in a multicenter study.

Therapy with Cardizem produced a low incidence of side effects.

In placebo-controlled trials (222 patients) conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with Cardizem in 959 patients in controlled and uncontrolled U.S. trials have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

Other reactions reported infrequently (less than 1%) are listed in full prescribing information on adjacent page.

Please see adjacent page for full prescribing information.

References:

1. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl): 234-238, 1980.
2. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.

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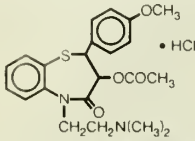
PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (four of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem tid of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to the drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY MISSOURI 64137

3/83

(Continued from Page 829)

MEDICINE

June 11-15—**American College of Physicians MKSAP Program.** Portland. Monday-Friday. Marriott Hotel. Contact: Postgraduate Dept., ACP, 4200 Pine Street, Philadelphia, PA 19104.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

PERINATAL MEDICINE

June 22-24—**Symposium on Perinatal Medicine.** Portland. Friday-Sunday. Thunderbird-Jantzen Beach. Contact: OHSU-CME.

SURGERY

July 8-11—**Practical Plastic Surgery for the Primary Care Physician.** Bend. Monday-Wednesday. Sunriver Resort. Contact: OHSU-CME.

December 7-8—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

June 1-2—**Orthopedics for the Primary Care Physician: Skeletal Problems of Childhood.** Portland. Friday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

June 22-23—**Exercise and Fitness.** Portland. Friday-Saturday. Red Lion-Lincoln Street. Contact: OHSU-CME.

September 7-8—**The Ashland Conference: Immunology and Allergy in Primary Care.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

(Continued on Page 840)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

(Continue from Page 830)

MEDICAL DIRECTOR—A 229 bed multi-level geriatric facility in Los Angeles is seeking full-time Medical Director. Candidate must have special education or training in Geriatric Medicine and must be qualified for an academic appointment. Duties include direct patient care, coordination of medical care in the facility, surveillance of employee health status, and supervision of UCLA School of Medicine geriatrics fellows. Competitive salary, and fringe benefits. For further information please contact Marilyn Green, Grancell Village of the Jewish Homes for the Aging, 7150 Tampa Avenue, Reseda, CA 91335.

PSYCHIATRISTS—Board certified or eligible to join staff of JCAH accredited CMHC and 32 bed Psychiatric Hospital in southeastern Washington state. Positions open: (1) Chief of 20 bed acute care adult unit with multi-disciplinary team approach, (2) outpatient psychiatrist to provide direct services and medical supervision for outpatient programs: med clinic, methadone, day treatment, etc. Share weekend call with five other psychiatrists. Opportunity for academic appointment. Excellent benefits, including 4 weeks paid vacation, one week paid CME, generous relocation allowance. Salary $55,000 to $70,000, incentive compensation for on-call. Area population approximately 140,000. Close to Cascade and Blue Mountains for skiing, camping, backpacking. Area offers excellent recreational activities. Clear, dry climate averaging 300 days sunshine per year. Send résumé to: Dr Peggy Pettit, Director of Hospital Services, Mid-Columbia Mental Health Center, 1175 Gribble Avenue, Richland, WA 99352. (509) 943-9104.

FAMILY PRACTITIONER—TULARE COUNTY, CALIFORNIA—Board certified Family Practitioner to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $75,779-$79,639 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266, An Affirmative Action Employer.

PEDIATRICIAN—TULARE COUNTY, CALIFORNIA—Board certified/eligible Pediatrician to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $79,639-$83,695 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291; (209) 733-6266. An Affirmative Action Employer.

INDUSTRIAL MEDICINE DIRECTOR responsible for medical direction new Industrial Medicine Clinic including market needs assessment, program development and service delivery to meet business/industry needs in greater Western Washington area. Will provide medical supervision of clinic operations including staff instruction in occupational medicine. Community relations activities will include public speaking, tours of client facilities. Must be Board certified or eligible with minimum four years experience in comparable position. Thorough knowledge federal/state regulations. Send curriculum vitae in confidence to Box 6427, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

RADIOLOGIST available for Locum Tenens during September or October 1984. Diagnostic Radiology, Nuclear Medicine, Ultrasound, no Angiography. Diplomate American Board of Radiology, California license, necessary insurance. Write: Clark-Bolitho P.C., 115 Lake Street, Manistique, MI 49854. Call: (906) 341-2164, 341-2074, or 283-3839

LOCUM TENENS SERVICE
WESTERN PHYSICIANS REGISTRY
. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

PHYSICIAN ASSISTANT—1982 graduate presently with burn/trauma unit and emergency dept. life flight. Also have experience in Family Practice and teaching/administration at university level. Seeking Surgical, Family Practice or Emergency Medicine position in rural or semi-urban area. Available immediately. CV on request. Jeff Birkinshaw, 2060 Hollywood, Salt Lake City, UT 84108; (801) 487-6328.

PHYSICIAN ASSISTANT AVAIL. 8 yrs exp. in FP and ER. Graduate of Hopkins PA program, NCCPA cert. and Calif license. M. Love, Rt. 1, Box 200, Show Low, AZ 85901; (602) 537-4865 after 6 p.m.

PAIN AND FAMILY PRACTITIONER seeks partnership with group or individual in California or southwestern states. (801) 583-5388.

GENERAL INTERNIST—position desired in Southern California group practice. Can start Steptember 1984. University trained and Board eligible. Reply Box 6423, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

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EXCELLENT PRACTICE OPPORTUNITIES in rural Northwest near the San Juan Islands and the North Cascades. Openings in Urology, Ophthalmology, Pediatrics and Family Practice. US medical school graduates only. Office space immediately available. For information call (206) 856-4522.

CALIFORNIA AND WESTERN STATES. HIGH INCOME practices for sale: Urology; Endocrinology, Radiology, Nephrology, Neurosurgery, Invasive and non-invasive Cardiology, OB/GYN, Psychiatry, Internal, Family, Pediatric, Surgery, others. Mary Bradshaw, Professional Practice Opportunities, 21 Altamount Drive, Orinda, CA 94563; (415) 376-0762. Sales, Appraisals, Consulting, Placement, Résumé preparation service.

AB CLINIC AND GYN PRACTICE. Gross $450,000+. Established, expandable, assumable financing arranged. (206) 527-4608.

FAMILY PRACTICE. Excellent opportunity. Retiring, gross $320,000, 4,000 sq ft bldg. w/lab, x-ray, etc. Ideal for clinic, group, emergency. Established 25 years. Negotiable. Don Mellman, (213) 656-3932.

FAMILY PRACTICE—Several locations within New Mexico. These are private-practice opportunities with income guarantee. Send CV to Dave Templeton, Southwest Community Health Services, Aubuquerque, NM 87102 or call 1 (800) 545-4030, extension 3050.

MD RESOURCES, INC.—A national physician search firm has several outstanding practice opportunities throughout the United States in Family Practice. For further information, please contact Penny J. Lamond toll free at 1 (800) 327-1585. MD Resources, Inc., 7385 Galloway Road, Suite 200, Miami, FL 33173.

NORTHERN UTAH, LOGAN: Internal Medicine practice available next to three year old hospital with CT scanner. 15K/mo gross, assume for $15K. (801) 753-0381.

CALIFORNIA, NEAR SAN JOSE, active Family Practice, well equipped office to rent or buy, accredited hospital, plan retirement. Write Box 6424, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

WELL ESTABLISHED FAMILY PRACTICE for sale. Puget Sound area. 1,600 ft clinic, well equipped, includes x-ray and lab, hospital near. Contact J. J. Erickson, MD, PO Box 44488, Tacoma, WA 98444.

FAMILY PRACTICE, established 23 year, Santa Ana Med. Office Bldg. 1,650 sq ft. Fully equip. incl. x-ray, bldg and practice excel. pk. price. Contact W. Hains, MD, 1610 W. Edinger, Santa Ana, CA 92704.

PROFESSIONAL PRACTICE SERVICES—Specializing in the sale and appraisal of practices in Sacramento and surrounding Northern Calif. areas. 884 Lincoln Way, Ste. 38, Auburn, CA 85603; (916) 823-2340.

ANESTHETIC MACHINE—Ohio Medical, 4000 Series, 'Compact,' fully equipped. 5 drawers w/lock. Like new. Reasonable. Dr Gilmartin, (916) 929-3686.

EXCELLENT PRACTICE OPPORTUNITIES in the university/resort town of Santa Cruz, California. Offices for rent on hospital grounds. Call Joanne Pearce, (408) 426-2080 for further information.

SEATTLE. N. Univ. for sale ideal building, location, zoning for individual/small group practice. 4,000+ sq ft, 8 rm, 2 bath house. See to appreciate value. Low 90's. By owner, Bruce Weller, (206) 523-7712, after 7 p.m.

MISSION VIEJO—1,200 sq ft professional furnished medical office with three exam rooms to share. Number of hours and days per week negotiable. Option to add another 460 feet for second consultation room and exam room if needed. Lease at $1.30 per foot if utilized for four days per week. Building is one year old and is across the street from Mission Community Hospital. (714) 644-1422.

PROFESSIONAL OFFICES FOR LEASE OR SALE in growing area of La Verne, California; 6 mo. free rent. Buy—low down payment. 635-7,344 sq ft. Call (714) 596-6555.

OFFICE SPACE AVAILABLE
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REDONDO BEACH
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Free standing Medical Building located in a prime residential and condominium area, close to three hospitals, and to the beach. Has been a medical office for over 30 years. 2,000 sq ft, many glass windows, lanai and patio. Ideal for one or two doctors and very suitable for time and day sharing especially for Pediatricians, Psychiatrists, GP/FPs, or other desiring idyllic surroundings for their patients instead of stone walls and forced air ventilation. Must be seen to be appreciated.

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William Bailey, MD
in care of Mr St. Clair
4001 Pacific Coast Highway, Suite 112
Torrance, CA 90505
PHONE: (213) 373-8896

THE AMERICAN ASSOCIATION OF COSMETIC SURGEONS ANNOUNCES

The International Congress for Hair Replacement Surgery
JUNE 14 - 16, 1984
Plaza Hotel, New York City

THE HAIR REPLACEMENT CONGRESS is an advanced seminar in hair replacement surgery with an innovative format on new and improved procedures by internationally known hair replacement surgeons. The program will feature multidiscipline speaker participants with keynote addresses, and panel and participant discussions. FREE PAPERS of 5 to 15 minutes in length are requested for selection. Send abstracts to: D. B. Stough, III, M.D., Congress Director.

For additional information, please contact: D. B. Stough, III, M.D.—Congress Director; The Stough Dermatology & Cutaneous Surgery Clinic, P.A.; Doctors Park; Hot Springs, AR 71901 (501) 624-0673.

HONORING NORMAN ORENTREICH, M.D., 25th ANNIVERSARY FOR HAIR TRANSPLANTATION

Program Advisory Committee: Thomas H. Alt, M.D.—Dermatology, Richard Grossman, M.D.—Plastic Surgery, Pierre Guibor, M.D.—Oculoplastic Surgery, Gaylon McCollough, M.D.—Facial Plastic & Reconstructive Surgery, Richard Webster, M.D.—Plastic Surgery.

THE ANNUAL SCIENTIFIC MEETING OF

The American Association of Cosmetic Surgeons
JUNE 16 - 17, 1984
Plaza Hotel, New York City

The American Association of Cosmetic Surgeons annual scientific meeting will be held following the International Congress for Hair Replacement Surgery. Robert Wood, M.D., P.S., Houston, Texas will be program director.

The annual meeting will discuss the most advanced techniques and trends in the following topics: Aesthetic Body Sculpting-Liposuction; Rhinoplasty; Facial Rejuvenation; Aesthetic Office Procedures; Aesthetic Procedures of the Eyelid.

For more information contact: Pierre Guibor, M.D., President, American Association of Cosmetic Surgeons, 630 Park Avenue, New York, New York 10021.

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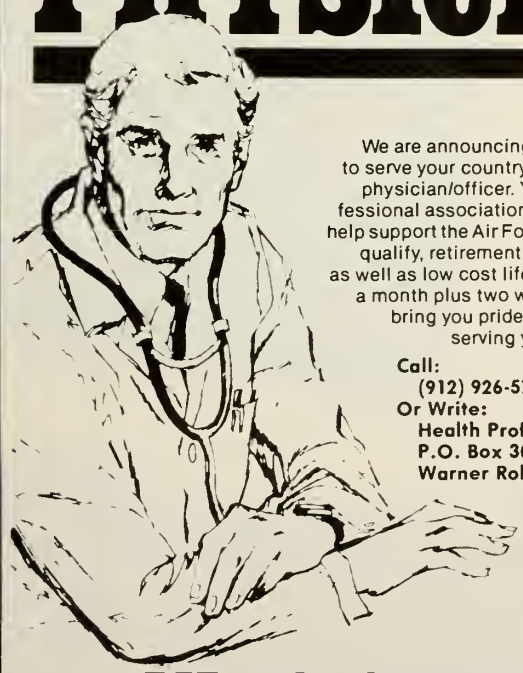

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A GREAT WAY TO SERVE

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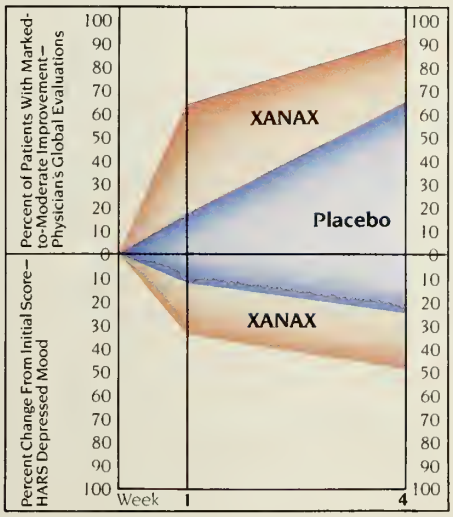
depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy

- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file, The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets

alprazolam Ⓘⓥ

XANAX® Tablets
(alprazolam) ©

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

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(Continued from Page 835)

First and third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7:00 a.m. to 9:00 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE GRAND ROUNDS

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Wednesday—8:00 a.m. to 9:00 a.m. Contact: Thomas Schwenk, MD, (801) 581-8633.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8:00 a.m. to 9:00 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8:00 a.m. to 9:00 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30 a.m. to 8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

(Continued on Page 842)

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(Continued from Page 840)

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext. 2143).

* * *

May 16—**Day in Nephrology at the University of Utah** (Sponsor: University of Utah). Wednesday. University Medical Center. 6 hrs. $30.00. Contact: Rosalie Lammle, (801) 581-8664.

June 3-6—**American Society for Lasers in Medicine and Surgery** (Sponsor: University of Utah). Monday-Wednesday. Salt Lake City. 8 hrs. Fee to be announced. Contact: John Dixon, MD, (801) 581-8201.

June 8-9—**Advanced Trauma Life Support (ATLS)** (Sponsor: University of Utah/Utah State Health Department). Friday-Saturday. Salt Lake Hilton Hotel. 14.5 hrs. $350. Contact: Kim Tanner, (801) 561-4594.

June 18-21—**School on Alcoholism and Other Drug Dependencies** (Sponsor: University of Utah). Monday-Thursday. University Medical Center. 26 hrs. $300. Contact: James Swenson, MD, (801) 581-7985.

July 15-20—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, Wyoming. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art** (Sponsor: University of Utah). Wednesday. Jackson Lake Lodge, Wyoming. Contact: John D. Armstrong, MD, (801) 581-7553.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 16-18—**Noise Measurement and Control.** Seattle. Wednesday-Thursday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

May 17—**Controversies in the Diagnosis and Treatment of Sleep Apnea.** Seattle. Thursday, 5 p.m. to 9 p.m. Providence Medical Center. $60 (includes dinner). Contact: Evelyn Foote, Physician Education, Providence Medical Center, 500 17th Ave., Seattle 98124. (206) 326-5555.

May 18—**Immunological Aspects of Allergies.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 24-25—**Hereditary Diseases of the Nervous System.** Seattle. Thursday-Friday. Mayflower Park Plaza. Contact: U/W.

May 25—**Monoclonal Antibodies in Cancer.** Seattle. Riverton Hospital. Contact: U/W.

May 31-June 2—**Office Hazards: Awareness and Control.** Seattle. Friday-Saturday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

June 1-2—**Advances in Cardiology—1984.** Bellevue. Friday-Saturday. Red Lion Inn. Contact: Nancy Aziz, MS, Overlake Hospital, 1035 116th Ave. NE, Bellevue 98004. (206) 454-4011, ext. 2630.

June 1-2—**Prenatal Diagnosis for the 80's.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: U/W.

June 2—**Eye Care for the Primary Physician.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, PO Box 900, Seattle, WA 98101. (206) 223-6898.

June 8—**Alcoholism: The Avoided Diagnosis.** Seattle. Friday. Virginia Mason Clinic. Contact: Mary Nolan, King County Medical Society, 200 Broadway, Seattle, WA 98122. (206) 621-9396.

June 8-9—**Fifth Annual Western Washington Cancer Conference.** Rosario Resort, San Juan Islands. Friday-Saturday. 9 hrs. Cat. I. $80. Contact: Annie M. Sakaguchi, Program Director, American Cancer Society, PO Box C-19140, Seattle 98109-1140. (206) 283-1152.

June 8-9—**Cardiology and Nephrology.** Seattle. Friday-Saturday. Museum of History and Industry. Contact: U/W.

June 9—**Recent Advances in Ultrasound.** Seattle. Saturday. U/W CDMRC. Contact: U/W Health Sciences, T-435.

June 13-15—**Use of Microcomputers in Occupational Safety and Health.** Seattle. Wednesday-Friday. Contact: Northwest Center for Occupational Health and Safety, Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

June 15-16—**Imaging Techniques and Computers in Radiation Therapy.** Seattle. Friday-Saturday. Sheraton. Contact: U/W.

June 15-17—**Nutrition Update for Clinical Dieticians.** Union. Friday-Sunday. Alderbrook Inn. Contact: U/W.

June 18-22—**Trauma: The First 3 Hours.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W.

June 21-22—**Stroke: Current Concept.** Seattle. Thursday-Friday. 8:30 a.m. to 5:00 p.m. Gould Auditorium. $150, physicians; $75, others. 12 hrs. Cat. I. Contact: Charlotte Kennedy, Northwest Hospital, 1550 N. 115th, Seattle 98133. (206) 364-0500, Ext. 1737.

June 23-27—(IDAHO) **Ethics at the Edges of Life.** Sun Valley. Saturday-Wednesday. Elkhorn. Contact: U/W.

July 4-10—(OREGON) **Medicine and Civilization.** Bend. Wednesday-Tuesday. Inn of the 7th Mountain. Contact: U/W.

July 10-13—(OREGON) **Medicine in Shakespeare's Time.** Ashland. Tuesday-Friday. Contact: U/W.

July 11-13—**Second Annual Conference on Occupational Hazards to Health Care Workers.** Seattle. Wednesday-Friday. Contact: Northwest Center for Occupational Health and Safety. Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 22-26—**Annual Summer Meeting 1984. Washington State Academy of Ophthalmology.** Orcas Island. Sunday-Thursday. Rosario Resort. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

July 27-29—**Seafair VI Pediatric Anesthesia and Intensive Care.** Seattle. Friday-Sunday. Seattle Sheraton. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave, Suite 900, Seattle 98121. (206) 623-4801.

August 29-September 4—(ALBERTA) **Scientific Aspects of the Art of Dance.** Banff Centre, Banff, Alberta. Contact: U/W.

September 12-14—**Dermatologic Therapeutic Hotline.** Orcas Island. Wednesday-Friday. Rosario Resort. Contact: Paul H. Jacobs, MD, Department of Dermatology, Stanford University Medical Center, Stanford, CA 94305. (415) 497-7854.

WYOMING

June 24-28—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Thursday. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 634-2424.

July 15-20—**Summer Update in Clinical Microbiology and Immunology.** University of Utah at Jackson Hole. Sunday-Friday. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art.** University of Utah at Jackson Lake Lodge. Wednesday. Contact: John D. Armstrong, MD, (801) 581-7553.

September 9-15—**Effective Management of Common Sports Injuries: An EPIC Medical Expedition.** Bicycle touring through Yellowstone and Grand Teton National Parks. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: June 8-12, 1984, Valdez Convention Center.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: 1985—date and place to be announced.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and Country, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 20-22, 1984, Mark Marriott, Vail.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: November 9-11, 1984, Kauai Surf Hotel, Kauai.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-28, 1984, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 3-6, 1984, Desert Inn, Las Vegas.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 2-4, 1984, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: 1985—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 24-28, 1984, Jackson Lake Lodge, Moran.

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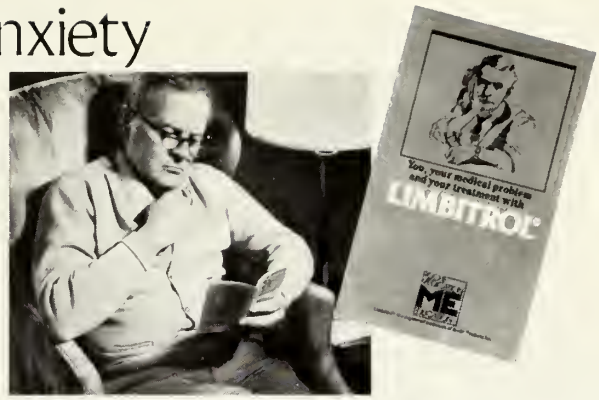
*Feighner JP: *Psychopharmacology 61* 217-225, Mar 22, 1979.



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In moderate depression and anxiety

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Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
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Rapid clearing through dual action

LIMBITROL® Tablets Ⓥ
Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female; elevation and lowering of blood sugar levels; and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)— bottles of 100 and 500. Tel-E-Dose* packages of 100, Prescription Paks of 50.

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Rapid clearing through dual action

Please see summary of product information on reverse side.

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The Western Journal of Medicine

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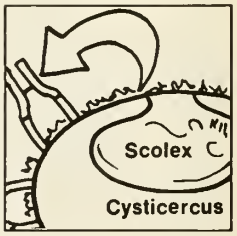

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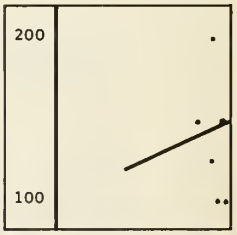

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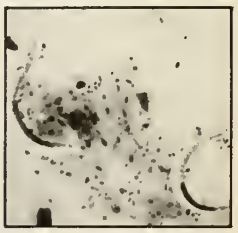

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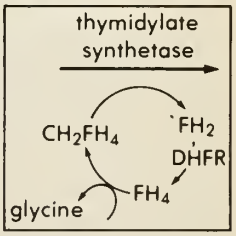

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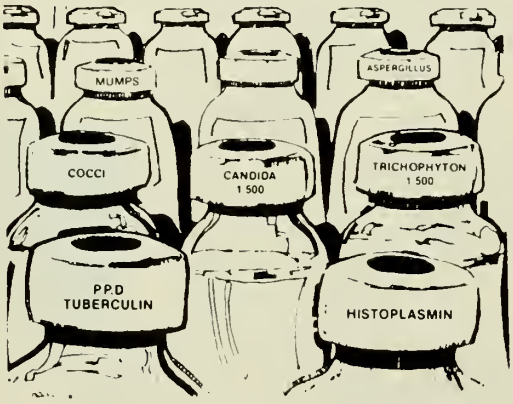

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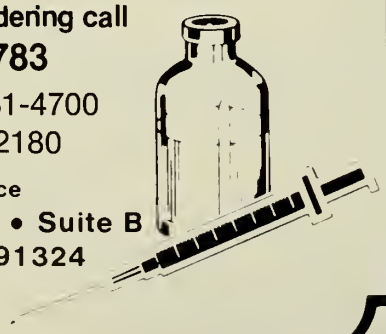

(Continued from adjacent page)

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNI-MATIC® unit-dose packs of 100 tablets.

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ACE* INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function*, Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on adjacent page)

INNOVATORS IN CARDIOVASCULAR MEDICINE

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Capoten®

(captopril tablets)

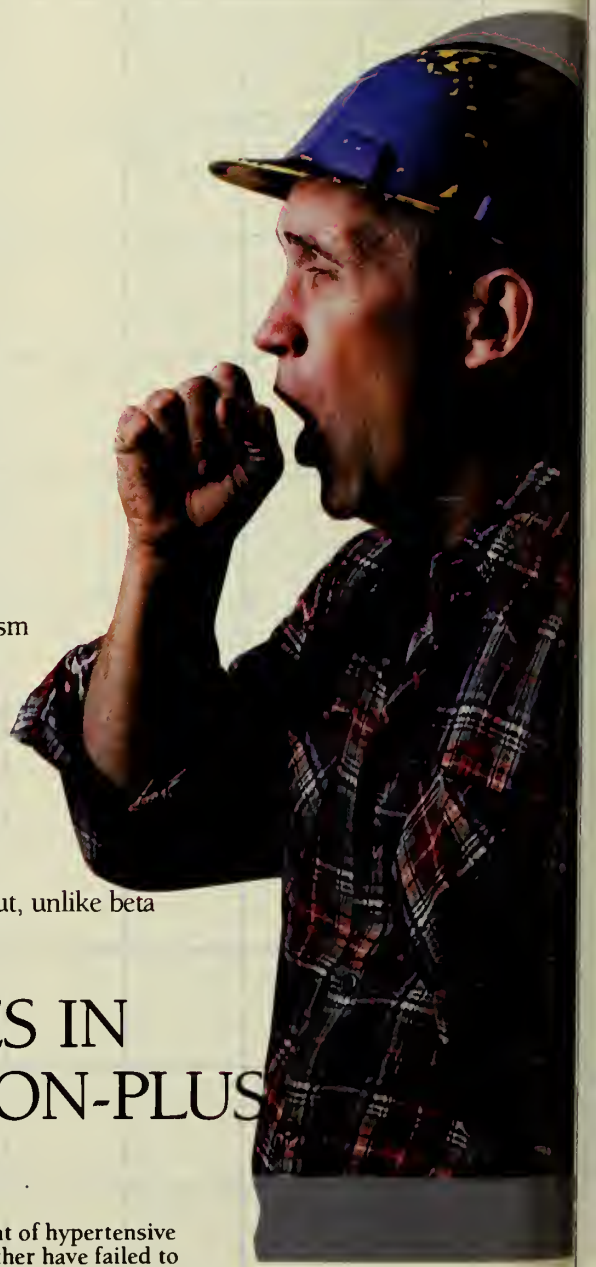
SQUIBB

FOR HYPERTENSION†-PLUS

Patients treated for hypertension† may have other disorders that commonly coexist with elevated blood pressure—approximately 14% may have diabetes, 7% asthma, 13% heart failure.[1] Unlike many other antihypertensive agents, CAPOTEN, because of its unique mode of action, is not contraindicated for use in any of these coexisting conditions that frequently complicate hypertension management:

+ DIABETES† (14%)

CAPOTEN does not mask the warning symptoms of hypoglycemia, unlike some beta blockers



+ BRONCHOSPASTIC PULMONARY DISEASE† (7%)

CAPOTEN rarely causes bronchospasm

+ HEART FAILURE† (13%)

CAPOTEN improves cardiac output, unlike beta blockers

MORE PLUSES IN HYPERTENSION-PLUS

*Angiotensin Converting Enzyme

†CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.

Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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929 **Kawasaki Disease**
EUNICE LARSON, MD

930 **Lyme Disease**
MARVIN L. WEIL, MD

930 **Pneumococcal Polysaccharide Immunization**
ARTHUR J. AMMANN, MD

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BARBARA F. CRANDALL, MD

931 **Growth Hormone Therapy**
DENNIS M. STYNE, MD

932 **Diagnosis and Management of Amebic Liver Abscess in Children**
JAMES SEIDEL, MD, PhD

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JOAN E. HODGMAN, MD

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Dr Baloh is Professor, Department of Neurology, University of California, Los Angeles, School of Medicine.

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FRANKLIN A. NEVA, MD
Dr Neva is Chief, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

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From the Department of Immunology and Infectious Diseases, Research Institute, Palo Alto Medical Foundation, Palo Alto, California, and the Division of Infectious Diseases, Department of Medicine, Stanford University School of Medicine, Stanford, California. Dr Gallagher is now affiliated with the Geisinger Medical Center, Danville, Pennsylvania.

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From the Departments of Medicine and Surgery, University of Utah School of Medicine, Salt Lake City.

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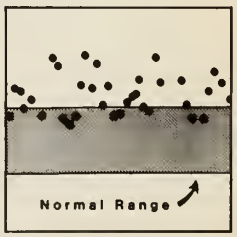
DAVID S. SCHADE, MD, and R. PHILIP EATON, MD
From the Division of Endocrinology and Metabolism, Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

951 **Enterococcal Endocarditis Following Flexible Sigmoidoscopy**
WILMER RODRIGUEZ, MD, and JOEL S. LEVINE, MD
From the Division of Gastroenterology, Department of Medicine, University of Colorado School of Medicine, Denver.



CORRESPONDENCE

954 **Less Cutting—More Treating?**
E. R. W. FOX, MD

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

October 4-6—**Allergy/Immunology.** UCSF. Thursday-Saturday.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Monday-Thursday. $375.

October 20—**Allergy Update—A Clinical Symposium.** Allergy Foundation of Northern California, Allergy Association of Northern California and the California Society of Allergy at Holiday Inn Union Square, San Francisco. Saturday. Contact: Dr. Chester Trossman, 500 E. Remington Dr., Sunnyvale 94087. (408) 730-0812.

October 24-28—**American Association for Clinical Immunology and Allergy Meeting** at San Diego. Wednesday-Sunday. Contact: Howard S. Silber, Exec. Dir., PO Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

October 25-28—**Allergy, Immunology and Infectious Disease.** Symposium Maui, Inc. and Hawaii Chapter American Academy of Family Physicians at Maui Marriott, Kaanapali, Maui. Thursday-Sunday. 18 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., PO Box 10185, Lahaina, Maui, HI 96761. (808) 661-8032.

ANESTHESIOLOGY

August 17-21—**Clinical Neuroanesthesia Conference.** UCSD at InterContinental Hotel, San Diego. Friday-Tuesday. 22 hrs.

September 28-30—**Anesthesia Practice 1984.** Anesthesiology Education Foundation at Monterey. Friday-Sunday. 10½ hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles 90024.

CANCER

June 15—**Cancer Precursors of the Cervix, Vagina and Vulva: An Overview of Pathogenesis and Management.** UCD at Red Lion Inn, Sacramento. Friday.

June 22—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing

(Continued on Page 859)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

Just once each day...

First-step blood pressure control with optimal simplicity

Benefits diuretics cannot offer... Once-daily INDERAL LA (propranolol HCl) provides smooth, 24-hour control of blood pressure plus the cardiovascular benefits of the world's leading beta blocker. And INDERAL LA provides a high degree of patient acceptance—without potassium problems.

Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

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Just once each day for initial therapy in hypertension.

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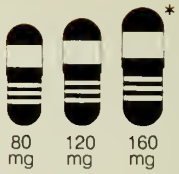
Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the platelets of the brain

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient But there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm

Propranolol is not significantly dialyzable
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL
WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol
PRECAUTIONS. *General* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories
8950/284

Ayerst. AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 855)

Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. $135. Contact: J. Shiller, CMEA, PO Box 94296, San Diego 92138. (619) 223-2997.

June 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 18-20—**8th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. $300. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

CARDIOLOGY

June 20—**Coronary Artery Disease Symposium.** UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday. 7 hrs.

June 22-24—**ECG Interpretation, Arrhythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at Lake Tahoe. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

June 22-24—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Scott and Klamath Rivers. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

June 25-27—**Cardiac Morphology: Echocardiographic, Nuclear Imaging, Necropsy Correlations.** American College of Cardiology and Indiana University School of Medicine at Hyatt Lake Tahoe, Incline Village. Monday-Wednesday. Contact: Reg. Sec., Extramural Programs Dept., ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

June 25-29—**National Board Review Course in Pulmonary Medicine.** American College of Chest Physicians at Sheraton Palace Hotel, San Francisco. Monday-Friday. 28 hrs. Contact: Dept. of Ed., ACCP, 911 Busse Hwy, Park Ridge, IL 60068. (312) 698-2200.

July 7-14—**Cardiovascular Medicine and Surgery and Critical Care Medicine.** STAN at Mauna Kea Beach Hotel, Kamuela. One week.

July 11—**Pulmonary and Intensive Care Medicine-Pulmonary Infections.** LLU. Wednesday.

August 12-17—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

August 17-19—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 24-26—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress and Holter) and Cardiac Resuscitation.** International Medical Education Corporation at Monterey. Friday-Sunday. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 14-16—**ECG Interpretation, Arrhythmia, and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 15-22—**Hawaiian Echocardiography Course.** Institute for Medical Studies at Hawaiian Islands. One week. 20 hrs. $295. Contact: IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

September 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Meridien Hotel, San Francisco. Thursday-Saturday.

October 7-10—**Cardiology Course**. UCSF at Yosemite. Sunday-Wednesday.

October 11-13—**Cardiology Update—1984.** ACC at Hyatt Del Monte Hotel, Monterey. Thursday-Saturday.

October 15-19—**Pulmonary Medicine Review 1984.** USC. Monday-Friday. $450.

October 26-28—**ECG Interpretation, Arrythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at San Francisco. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

(Continued on Page 863)

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MUTUAL PROTECTION TRUST
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Active duodenal ulcer healing through effective acid control

- ☐ Just one tablet every twelve hours effectively controls acid secretion day and night—b.i.d. dosing*
- ☐ Effective duodenal ulcer healing in 2**-4 weeks.
- ☐ No interaction with warfarin, theophylline or diazepam.
- ☐ Headache has been reported in about 3% of patients.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers. Despite some similarities in pharmacokinetics, after 10-12 hours Zantac 150 mg still provides a 40% reduction in acid output compared to 1% for cimetidine 300 mg, thus providing a rationale for b.i.d. dosing.

** 37% of patients can be expected to show complete healing at the end of two weeks; if healing is confirmed, treatment can be discontinued.

Glaxo ROCHE

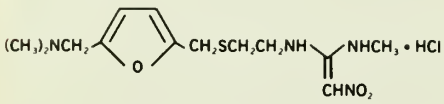
Please see complete prescribing information on the following page.

The first advance in H_2-antagonist therapy

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTIDN: The active ingredient in ZANTAC* Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure:



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLDGY: ZANTAC* (rantidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. Effects on acid secretion:

ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC* on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. Effects on other gastrointestinal secretions:

Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice.

Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. Other pharmacological actions:

a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. Pharmacokinetics:

ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Duodenal Ulcer

In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC*-treated patients as shown below:

	ZANTAC* +		Placebo +	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid	
	Ulcer Healed	Ulcer Not Healed
ZANTAC*	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)

ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIDNS AND USAGE:

ZANTAC* (ranitidine hydrochloride) is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC* (ranitidine hydrochloride).

PRECAUTIDNS:

General

1. Symptomatic response to ZANTAC* therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests

False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction

Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility

There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, E. Coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC* (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS

Headache has been found to be more frequent in ZANTAC*-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

DVERDDSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC* in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DDSAGE AND ADMINISTRATIDN:

Duodenal Ulcer

The current recommended adult oral dosage of ZANTAC* for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HDW SUPPLIED

ZANTAC* Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

(Continued from Page 859)

EMERGENCY MEDICINE

June 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton Wharf, San Francisco. Monday-Friday. $425.

July 4-5—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Salmon River. Wednesday-Thursday. 10 hrs. $245. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

July 6-8—**Trauma and CPR Update—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 10-13—**Emergency Medicine: A Critical Appraisal.** California Chapter American College Emergency Physicians and Emergency Medical Associates at Ramada Inn at Fisherman's Wharf, San Francisco. Tuesday-Friday. 20 hrs. $360. Contact: Seminars International, Dept. A, 15910 Ventura Blvd., Ste. 731, Encino 91436.

July 16-20—**Postgraduate Institute for Emergency Physicians.** UCSD. Monday-Friday. 33 hrs.

July 30-31—**Advanced Cardiac Life Support.** Emergency Care Education Center, Emergency Department Physicians, and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina Del Rey 90291. (213) 822-1312.

August 3-5—**Whitewater Raft Conference: Trauma Evaluation and Treatment.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** American College of Obstetrics and Gynecology at Hotel del Coronado, Coronado. Wednesday-Friday. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 24-26—**Wilderness Emergency Care—Mt.**

(Continued on Page 867)

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954 **Oral Contraceptives and Six Benign Liver Tumors—The Mestranol Question**
A. DAVID BARNES, MD, MPH; RONALD P. HATTIS, MD, MPH, and PAUL J. TOOT, MD

955 **Artificial Solutions to Health Care Problems**
ROBERT E. HOLLIS, MD

955 **Nutritional Aspects of Cross-cultural Medicine**
CHRISTINE S. WILSON, PhD

956 **Passive Smoking—Corrections in Tables of April Article**
G. H. MILLER, PhD

TOPICS IN PRIMARY CARE MEDICINE

957 **Headache—Diagnosis and Effective Management**
KENNETH S. PETERS, MD
Dr Peters is Medical Director, Northern California Headache Clinic, Mountain View, California.

MEDICINE AND GOVERNMENT

961 **Local Perceptions of Federal Block Grants**
ROBERT F. TOMFOHRDE, MD, and LAURIE A. SOMAN, MSW
Dr Tomfohrde is in private practice in Berkeley, California, and Chair of the California Medical Association Committee on Block Grants; Ms Soman is Staff Assistant for the Committee on Block Grants.

COMMENTARY

964 **Health Belief Systems and the Psychobiology of War**
NEIL J. ELGEE, MD
Dr Elgee is Clinical Professor of Medicine, University of Washington School of Medicine, Seattle.

PUBLIC HEALTH

969 **Death in the West—A Regional Analysis of the Youthful Suicide Rate**
RICHARD H. SEIDEN, PhD, MPH
From the Department of Social and Administrative Health Sciences, University of California School of Public Health, Berkeley.

OTHER FEATURES

855 **Continuing Medical Education Activities in California, Hawaii and Nevada; Alaska; Idaho; Montana; New Mexico; Oregon; Utah; Washington; Wyoming**

881 **Idaho Medical Association Annual Meeting**

974 **In Memoriam**

Book Reviews

975 **Hypoglycemia: Fact or Fad?—What You Should Know About Low Blood Sugar**
LYNN J. BENNION, MD
Reviewed by JOHN H. KARAM, MD

975 **Watson-Jones Fractures and Joint Injuries**—2 Volumes: 6th Edition
Edited by J. N. WILSON, ChM, FRCS
Reviewed by MARVIN B. HAYS, MD

976 **Volume Index**

988 **Subscription Information**

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★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: The Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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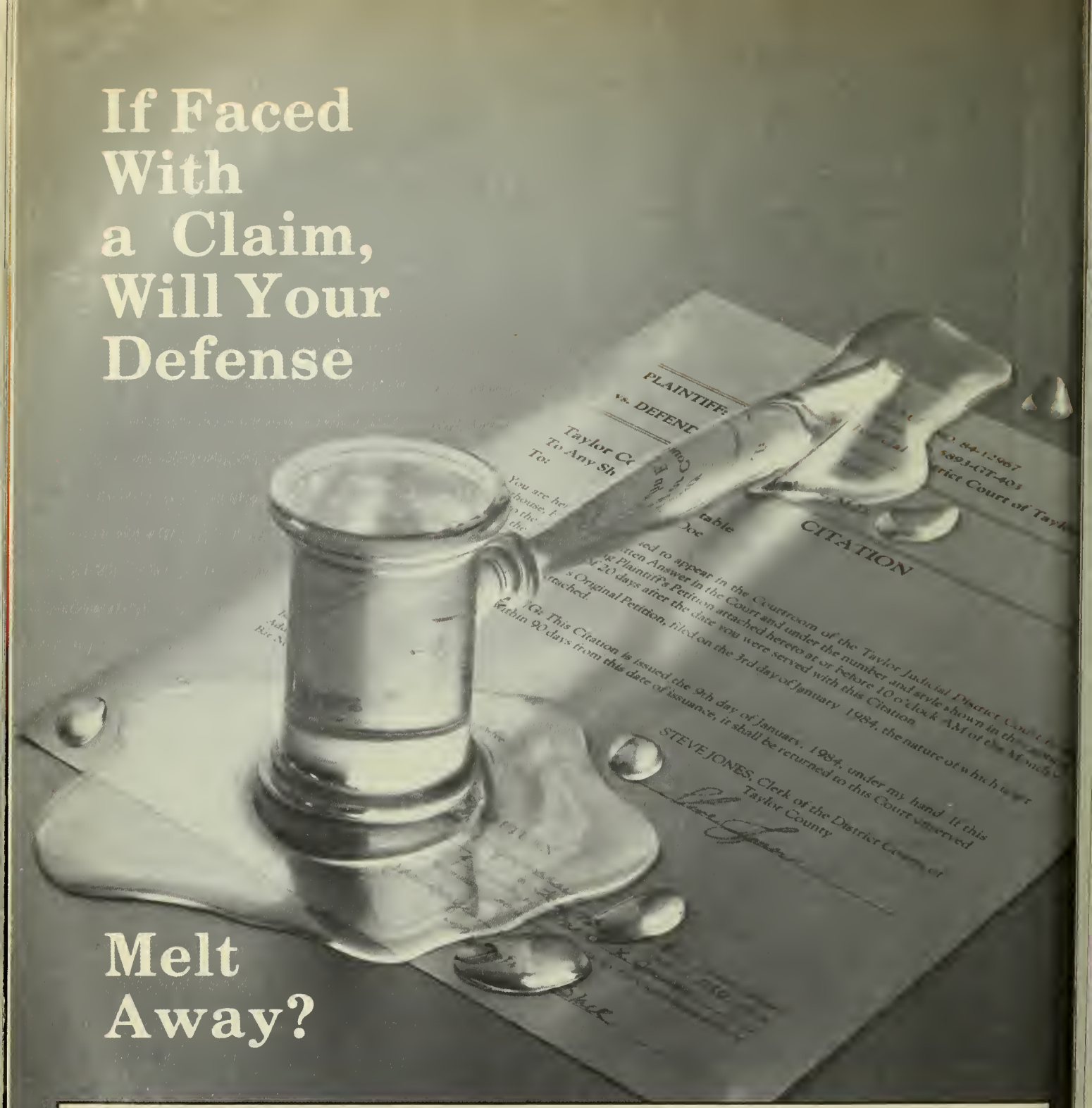

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(Continued from Page 863)

Shasta Summit Expedition. Mercy Medical Center, Redding at Mt. Shasta. Friday-Sunday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 27-31—**Topics in Emergency Medicine.** UCSF at San Francisco. Monday-Friday. $425.

September 1-3—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Klamath River. Saturday-Monday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

September 6-7—**Burns: Emergency and Acute Care.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Friday.

September 17-21—**Postgraduate Institute for E.R. Physicians, Symposium I.** UCSD at InterContinental Hotel, San Diego. Monday-Friday. 36 hrs.

September 28-29—**Advanced Trauma Life Support Provider Course.** Emergency Shock Trauma Institute, Mercy Hospital at San Diego. Friday-Saturday. 16 hrs. $475. Contact: Emergency Shock Trauma Institute, Mercy Hospital, 4077 5th Ave., San Diego 92103. (619) 294-8111.

October 29-30—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

October 31-November 2—**EMS Today.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 19 hrs.

INTERNAL MEDICINE

June 18-22—**Advances in Internal Medicine.** UCSF. Monday-Friday. $465.

June 22-24—**Update on Cardiovascular Drugs—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

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July 7-14—**32nd Annual Intensive Review of Internal Medicine.** USC. One week. $475.

July 20-22—**Infectious Disease.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 29-August 1—**Biomedical Ethics—Wilderness Horseback Conference.** Mercy Medical Center, Redding at Trinity Alps Wilderness. Sunday-Wednesday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 17-19—**2nd Annual La Jolla Summer Conference on Dermatology, Immunology and Rheumatology.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. Contact: Dianne Tisue, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

September 1-2—**Thyroid Today—1984: 3rd Annual Symposium.** See Of Interest to All Physicians, September 1-2.

September 10-15—**6th Comprehensive Nephrology Review Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Saturday. 38.5 hrs. $695.

September 15—**Neurology.** UCSF at Fresno. Saturday.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 19—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. Contact: Charles R. Beeson, MD, Assoc. Chief of Staff for Ed., VA Medical Center, 16111 Plummer St., Sepulveda 91343. (818) 891-2374.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** See Allergy and Immunology, October 15-18.

October 17—**Diabetes—1984.** The Hospital of the Good Samaritan at Hyatt Regency Hotel Los Angeles, Los Angeles. Wednesday. Contact: Dolores Gay, Coordinator of Symposia, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

OBSTETRICS AND GYNECOLOGY

June 15—**Cancer Precursors of the Cervix, Vagina and Vulva: An Overview of Pathogenesis and Management.** See Cancer, June 15.

June 21-23—**Gynecologic Surgery: Principles and Techniques.** See Surgery, June 21-23.

August 9-11—**Basic and Advanced Colposcopy.** American College of Obstetrics and Gynecology at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 12—**OB/GYN—Menstrual Disorders.** LLU. Wednesday.

October 6—**Clinical Ultrasound—OB/GYN Update.** Sacramento Radiology Research and Education Foundation and the Northern California Radiology Society. Saturday. $75. Contact: J. P. McGahan, MD, Program Director, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 7-9—**The Neural and Metabolic Bases of Feeding.** See Pediatrics, October 7-9.

October 22-27—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** UCI. Monday-Saturday.

OPHTHALMOLOGY

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** See Pediatrics, June 29-30.

July 14—**Update for Nonophthalmologists: Ocu-**

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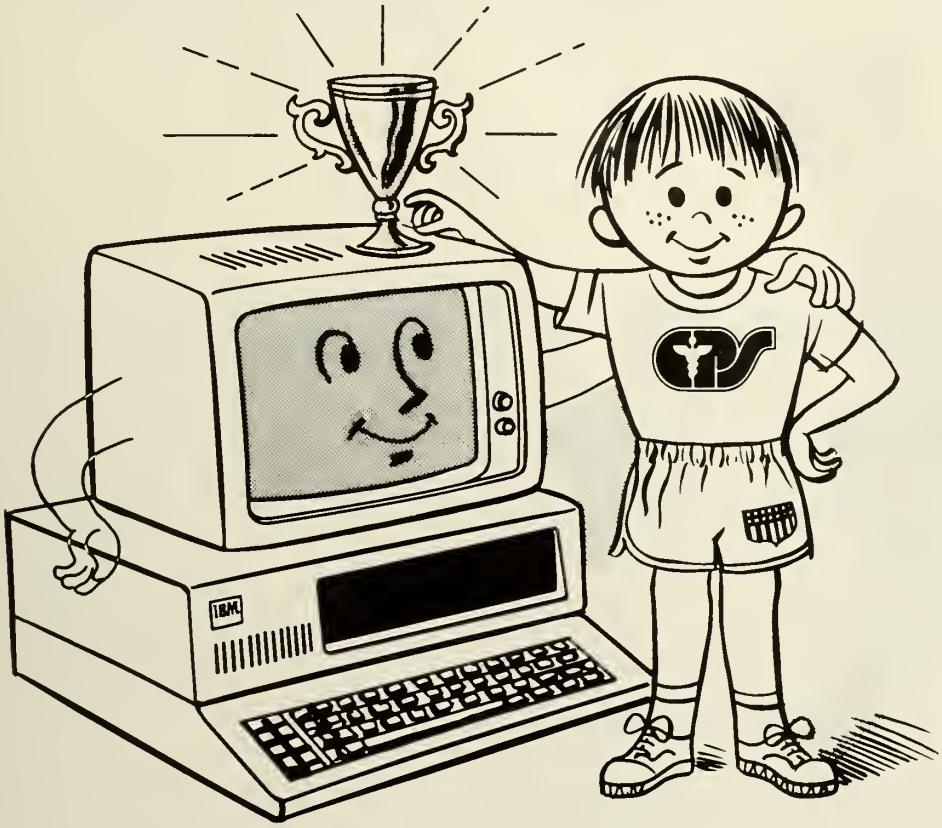

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0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS

The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

■ = objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

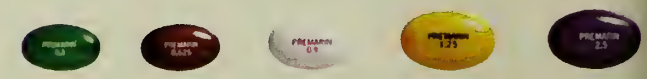
Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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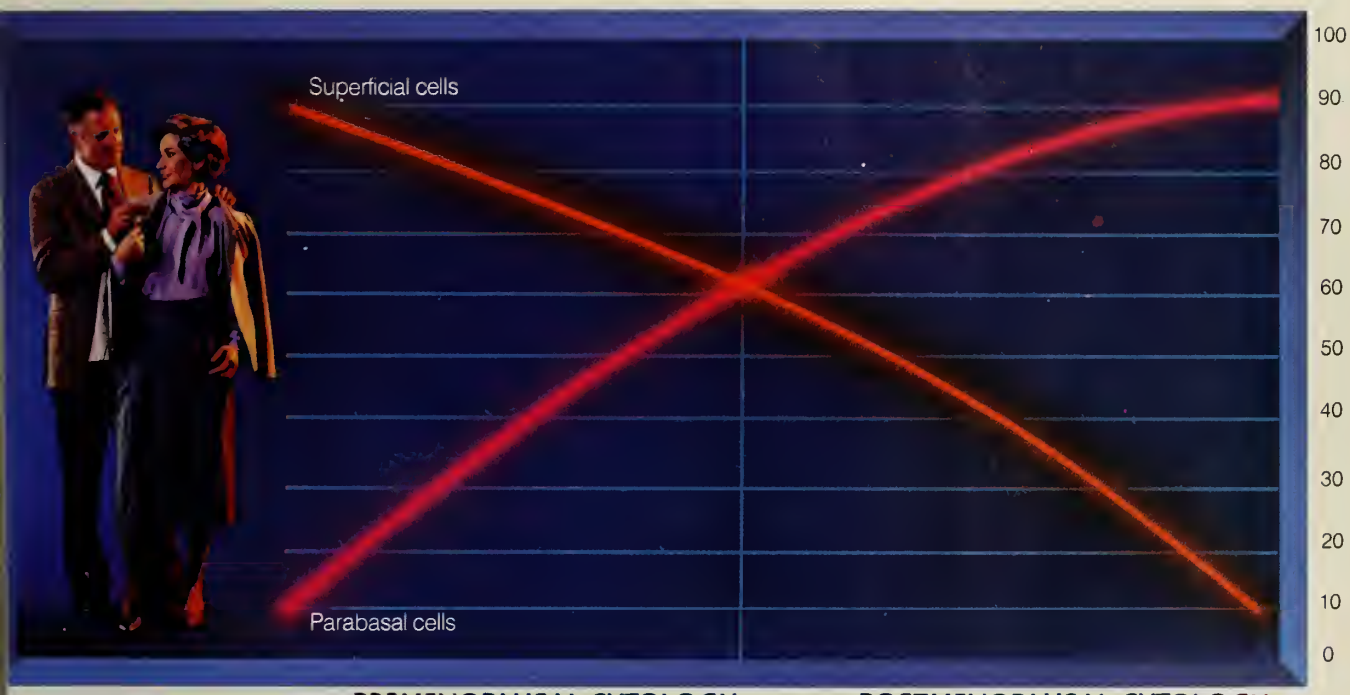
THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

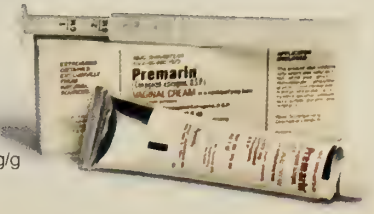
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

FOR ATROPHIC VAGINITIS

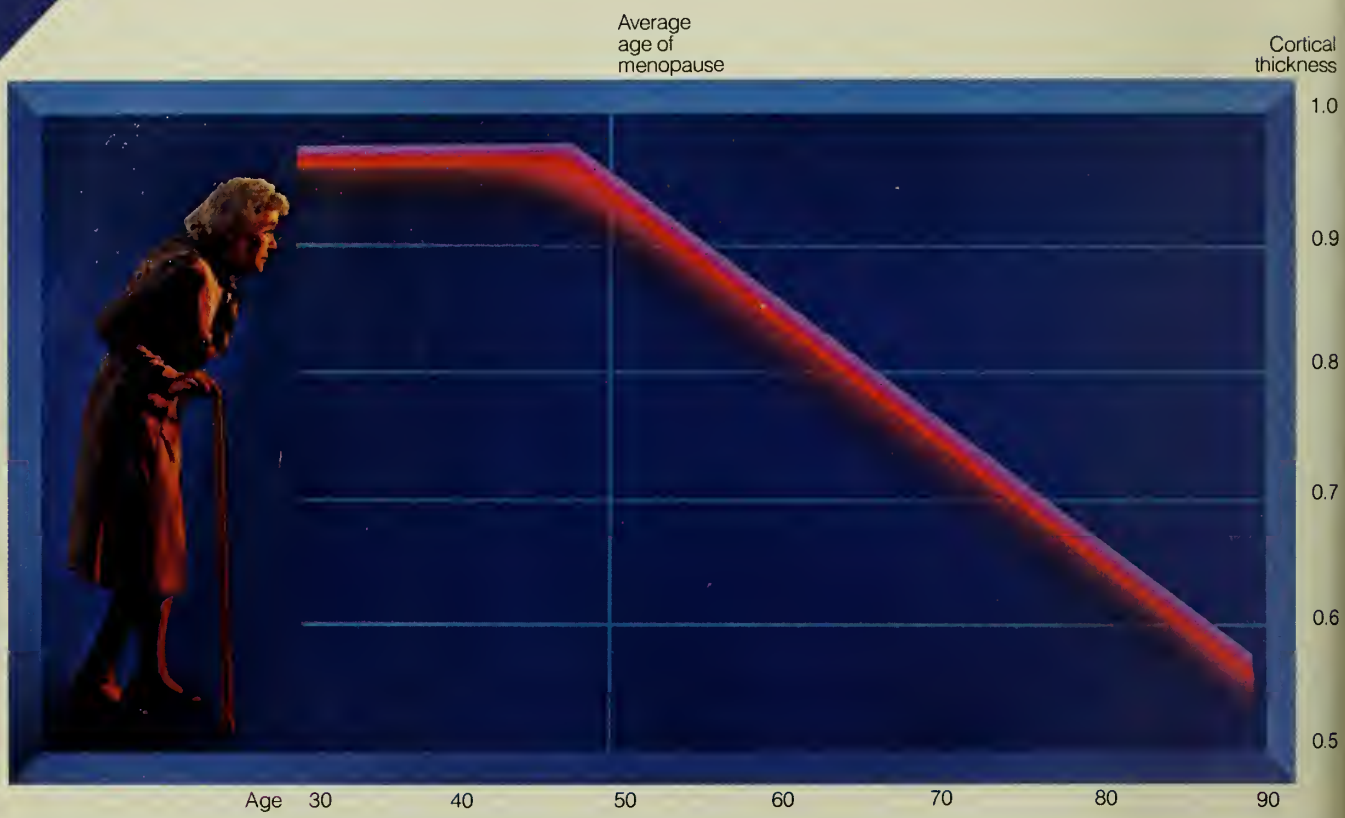
PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/g

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration, it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma – palliative therapy of advanced disease.
9. Postpartum breast engorgement – Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism, steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism – 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure – 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression) – 1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement – 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer – 1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women – 10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865 – Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 – Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864 – Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867 – Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868 – Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream – No. 872 – Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available – Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube.

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(Continued from Page 868)

lar Complications in Syphilis, AIDS and Other Inflammatory Diseases. JSEI. Saturday.

July 26-27—**Ophthalmology Symposium.** UCI. Thursday-Friday.

August 25—**Neodymium: YAG Laser Workshop.** JSEI. Saturday.

October 10—**Ophthalmology-Therapeutic Decision re: Glaucoma, Retinopathy and Cataracts.** LLU. Wednesday.

October 11-13—**Cosmetic Blepharoplasty Workshop.** JSEI. Thursday-Saturday.

October 20—**Update for Nonophthalmologists: Ocular Diseases of Aging.** JSEI. Saturday.

PEDIATRICS

June 28-30—**9th Annual Meeting of the Society for Pediatric Dermatology.** STAN at Caesar's Tahoe, Lake Tahoe. Thursday-Saturday.

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Saturday. 8 hrs. $100.

October 3-4—**41st Annual Brenneman Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Red Lion Motor Inn, Sacramento. Sunday-Tuesday.

October 26-27—**Adolescents Inside and Out.** Children's Hospital Medical Center of Northern California and California Chapter 1 of the American Academy of Pediatrics at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes-Dodd, Medical Staff Office, Children's Hospital Medical Center, 51st and Grove St., Oakland 94609. (415) 428-3334.

PSYCHIATRY

June 16—**Clinical Decision-Making with Couples and Families.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

June 18-22—**Divorce Mediation.** Mental Research Institute, Palo Alto. Monday-Friday. 20 hrs. $195. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 14—**The Interactional Treatment of Eating Disorders.** Mental Research Institute, Palo Alto. Saturday. 7 hrs. $95. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 20-21—**Human Sexuality for the Health Professional.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 23-27—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 28—**Treating Depression in a Marital Context.** Mental Research Institute. Palo Alto. Saturday. 5 hrs. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 29-August 2—**Mental Research Institute Summer Seminar** at Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-8—**Basic Hypnotherapy: Principles and Applications.** Mental Research Institute, Palo Alto. Monday-Wednesday. 6 hrs. $65. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-10—**Brief Therapy.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $175. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 8—**Continuing Medical Education Seminars—Psychiatry.** LLU. Wednesday.

August 13-16—**Family Crisis: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 18-23—**Responsibility Issues in Mental Health.** Southern California Psychiatric Institute at Mauna Kea Beach Hotel, Kauela, HI. Saturday-Thursday. 15 hrs. Contact: Gail

(Continued on Page 876)

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(Continued from Page 874)

Waldron, MD, Program Dir., SCPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

August 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 25—**Case Studies in Brief Interactional Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

RADIOLOGY AND PATHOLOGY

June 17-22—**Pathology of the Lung.** UCSD. Sunday-Friday. 50 hrs.

August 20-24—**Radiology of the Abdomen.** UCSD at San Diego and Anaheim. Monday-Friday. 27 hrs. $395.

August 27-29—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and Northern California Radiological Society at Napa Valley. Monday-Wednesday. 18 hrs. $325. Contact: Michael H. Reid, MD, Program Dir., SRREF, PO Box 19184, Sacramento 95819.

September 6-9—**Radiology Physics Review Course.** UCD at Sacramento. Thursday-Sunday.

September 17-20—**American College of Radiology Meeting** at Century Plaza Hotel, Los Angeles. Monday-Thursday. Contact: ACR, 20 N. Wacker Dr., Chicago 60606. (312) 236-4963.

October 13-21—**9th Annual International Body Imaging Conference.** West Park Hospital at Royal Lahaina Hotel, Maui. One week. 28 hrs. $425. Contact: Conference Sec., 9th Annual Body Imaging Conf., Dept. of Radiology, West Park Hospital, 22141 Roscoe Blvd., Canoga Park 91304. (818) 340-0580, ext. 280.

October 22-26—**9th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Monday-Friday.

(Continued on Page 885)

RU-TUSS® II
sustained release capsules

Before prescribing, see complete prescribing information. The following is a brief summary.
DESCRIPTION: Each sustained release capsule contains 12 mg of chlorpheniramine maleate, USP and 75 mg of phenylpropanolamine hydrochloride, USP in a base to provide prolonged activity.
INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).
CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.
WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.
Usage in pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.
PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.
ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with chlorpheniramine maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, hypertension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis, leukopenia.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis hysteria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.
DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.
OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.
HOW SUPPLIED: Green and clear capsules with green and white beads. Bottles of 100 tablets. NDC 0524-0031-01
Store at controlled room temperature 15-30°C (59°-86°F.).
CAUTION: Federal law prohibits dispensing without prescription.

Distributed By
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Shreveport, LA 71106

Manufactured By
Cord Laboratories, Inc.
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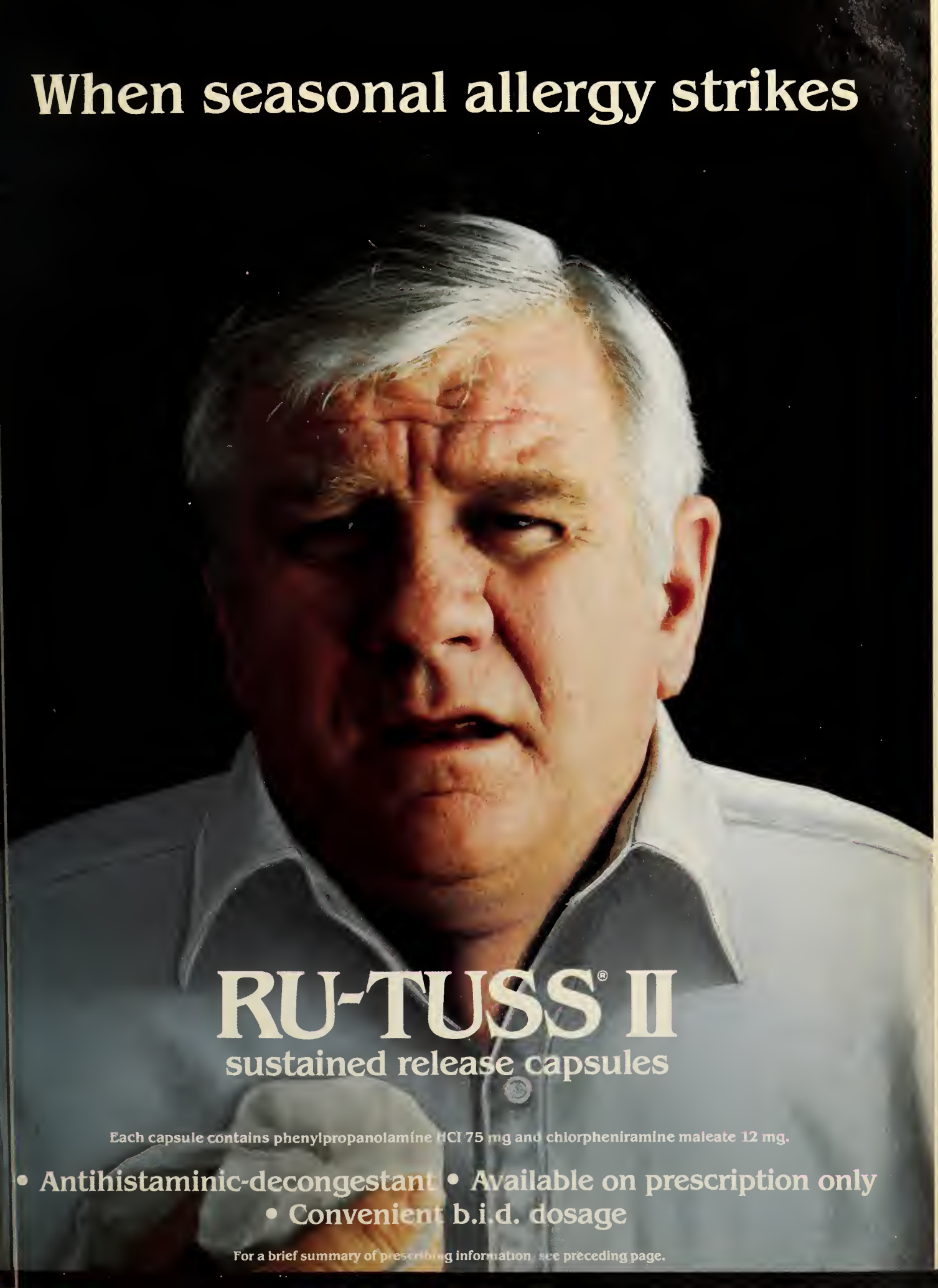
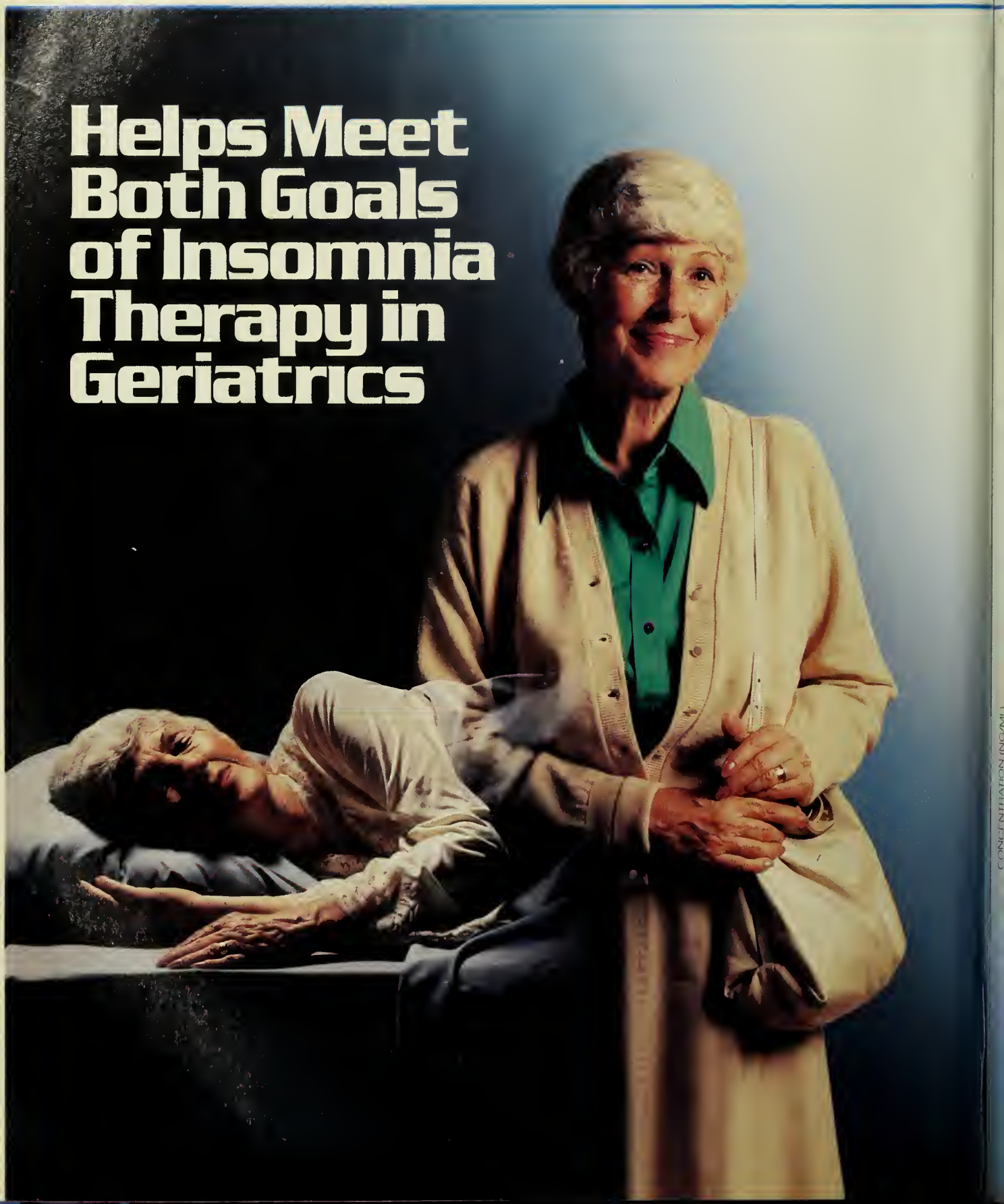
Boots Pharmaceuticals, Inc.
Shreveport, LA 71106
Pioneers in medicine for the family

When seasonal allergy strikes

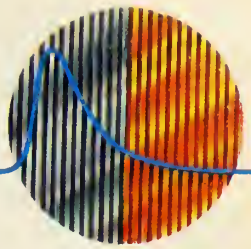


Halcion® 0.25 mg Tablets

triazolam CIV



Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion

triazolam IV

0.25 mg Tablets
Initiate at 0.125 mg

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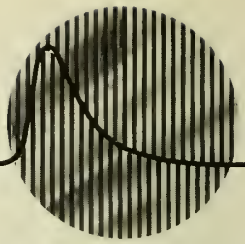
Halcion Tablets
triazolam (IV)



Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion,* initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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Kalamazoo, Michigan 49001 USA

IDAHO MEDICAL ASSOCIATION

92nd Annual Meeting

July 25-28, 1984 • Sun Valley, Idaho

AN INVITATION TO SUN VALLEY JULY 25-28, 1984

We are pleased to extend to you a cordial invitation to attend the 92nd Annual Meeting of the Idaho Medical Association in the beautiful setting of Idaho's Sun Valley. An excellent scientific session has been planned that should appeal to all types of physicians, family practitioners and specialists alike. It should be a good opportunity not only to enjoy beautiful Sun Valley, but also receive 8 credit hours of Category I at an informative scientific session.

WILFRED E. WATKINS, MD
President, Idaho Medical Association

92nd Annual Meeting
Idaho Medical Association
Sun Valley—July 25-28, 1984

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Depart _____, 1984 at _____.

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- ☐ Two-Bedroom, $130 to $180 per day
- ☐ Three-Bedroom, $155 to $230 per day

Each additional person $10

CANCELLATIONS: *No deposit refunds on cancellations received less than 7 days prior to arrival. There is a $10 per person processing charge on all cancellations.*

IDAHO MEDICAL ASSOCIATION

92nd Annual Meeting

JULY 25-28, 1984

WEDNESDAY, JULY 25, 1984

9 am-5 pm HOUSE OF DELEGATES

THURSDAY, JULY 26, 1984

SCIENTIFIC SESSION

9:00 am WELCOME
Wilfred E. Watkins, MD, President, IMA

9:15 am PYELONEPHRITIS, "THE RUINED KIDNEY"
Russell B. Roth, MD

10:00 am "NEW" PNEUMONIAS
Barbara Kirby, MD

11:15 am EMERGENCY ROOM DERMATOLOGY
Don E. Gehle, MD

1:30 pm MORBIDITY AND MORTALITY IN MYCOPLASMAL PNEUMONIA
Barbara Kirby, MD

2:15 pm NON-BACTERIAL PROSTATITIS
Russell B. Roth, MD

3:30 pm NON-VIRAL, NON-REPORTABLE SEXUALLY TRANSMITTED DISEASES
Barbara Kirby, MD

4:15 pm LOTIONS, POTIONS AND NOTIONS
Don E. Gehle, MD

FRIDAY, JULY 27, 1984

8:45 am INTRODUCTION
James J. McCabe, MD, Chairman, IMA Program Committee

9:00 am SEXUALLY TRANSMITTED DISEASES
Don E. Gehle, MD

10:15 am COMPUTERS IN THE MEDICAL OFFICE
PANEL: **Gary Dyer,** Director of Electronic Data Processing, Blue Cross of Idaho, Boise, Idaho
William H. Engle, Vice President, Internal Operations, Blue Shield of Idaho, Lewiston, Idaho
William Larson, Executive Vice President, Technical Service Inc., (a Subsidiary of Multnomah County Medical Society), Portland, Oregon
Joseph Karpach, Field Director
Equitable Life Assurance/Medicare, Boise, Idaho

11:15 am DRGs
Russell B. Roth, MD

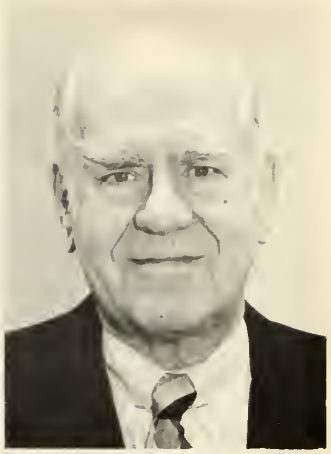
SATURDAY, JULY 28, 1984

8:30 am CLOSING SESSION, HOUSE OF DELEGATES

REGISTRATION FEE $125 FOR NON-IMA MEMBERS AND OUT-OF-STATE PHYSICIANS.

For information contact:

IDAHO MEDICAL ASSOCIATION
P.O. BOX 2668
BOISE, IDAHO 83701 TELEPHONE: (208) 344-7888

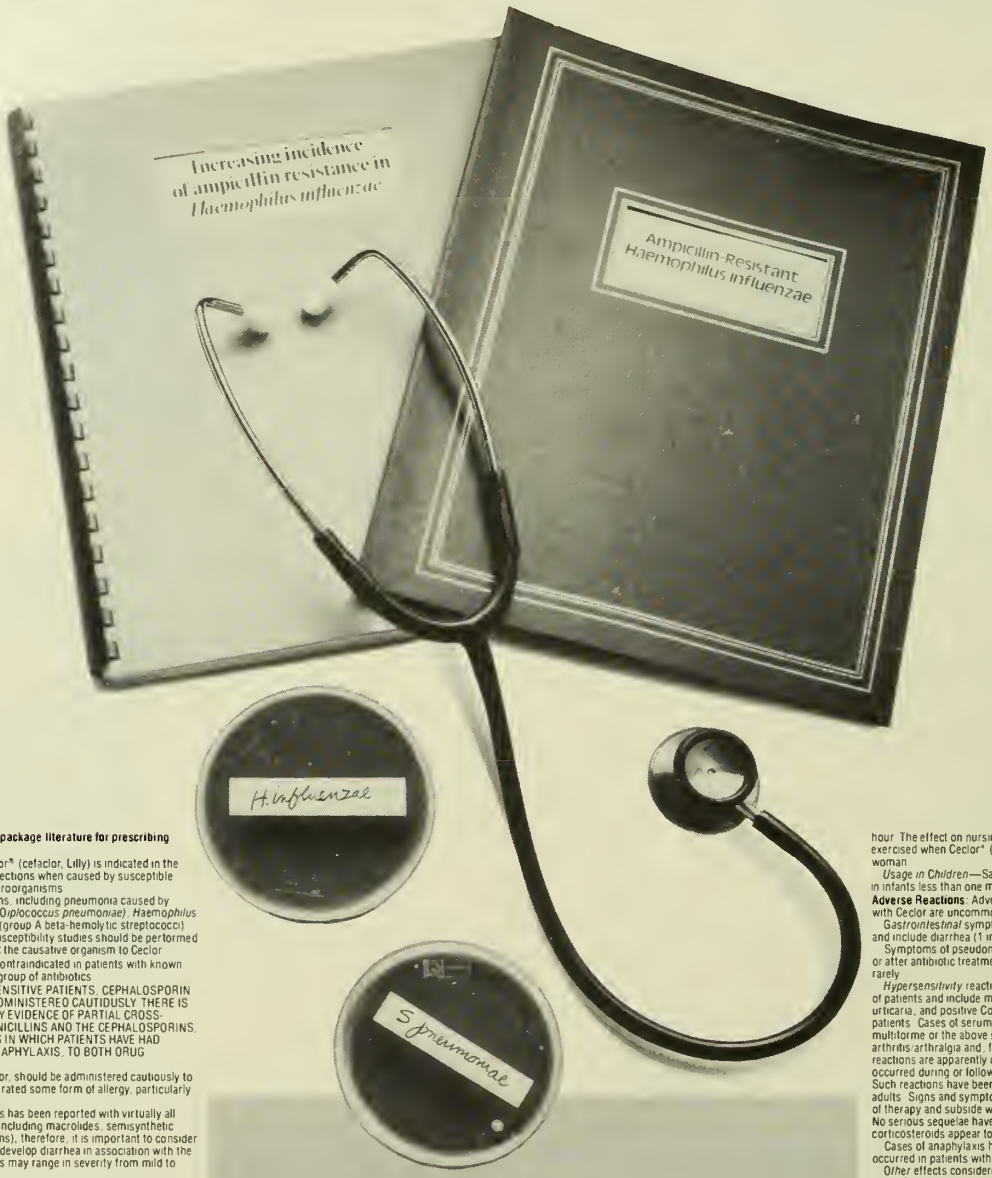


Russell B. Roth, MD
Past President, AMA;
Past President, American Association of Clinical Urologists,
Erie, Pennsylvania

Don E. Gehle, MD, COL, MC
Chief, Dermatology Service
Madigan Army Medical Center
Tacoma, Washington

Barbara D. Kirby, MD
Assistant Professor of Medicine
University of Washington
Seattle, Washington

An added complication... in the treatment of bacterial bronchitis*



Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

References

1. Antimicrob. Agents Chemother., 8:91, 1975
2. Antimicrob. Agents Chemother., *11*:470, 1977
3. Antimicrob. Agents Chemother., *13*:584, 1978
4. Antimicrob. Agents Chemother., *12*:490, 1977
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob. Agents Chemother., *13*:861, 1978
7. Data on file, Eli Lilly and Company
8. Principles and Practice of Infectious Diseases (edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett), p. 487. New York: John Wiley & Sons, 1979

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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Computerized Aftercare Instructions by Medical Microsystems are software programs which generate complete, comprehensive instructions concerning prescription information and aftercare information for patients discharged from physicians' offices, clinics and emergency facilities. "AFTERX", "INFORX", and "RXWRITE" are patient instruction programs on floppy discs, available for MS-DOS (IBM & compatible), TRS DOS (RADIO SHACK), and CP/M86 operating systems. Programs are explained in such a way that previous computer operator experience is not required.

"AFTERX" consists of patient aftercare instructions for up to 60 clinical situations or conditions. The instructions are readable by persons with an 8th grade education and the program is available in English and Bilingual versions (English/Spanish).

"INFORX" contains patient prescription information with appropriate special instructions for taking and storing medications as well as information on common side effects and reactions. It is available with an optional prescription printing module.

"RXWRITE" is a combined program of the above two. A drug interaction module will be available in the summer of 1984.

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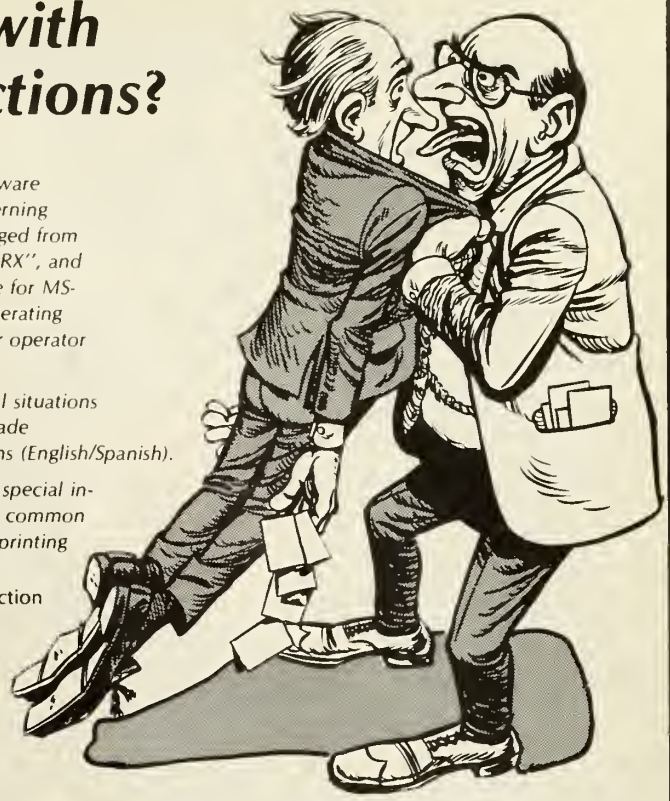

CONTINUING MEDICAL EDUCATION

(Continued from Page 876)

SPORTS MEDICINE

June 24-27—**Marine Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Wednesday.

July 20-22—**Sports Medicine and Cardiovascular Fitness—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 23-26—**10th Annual Meeting of American Orthopaedic Society for Sports Medicine** at Marriott Hotel, Anaheim. Monday-Thursday. Contact: AOSSM, PO Box 94274, Chicago 60690.

SURGERY

July 9-13—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

June 9-14—**Fingers to the Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Saturday-Thursday.

June 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 20-24—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Regency, Maui. Wednesday-Sunday. Contact: WTSA, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

June 21-23—**Gynecologic Surgery: Principles and Techniques.** American College of Obstetrics and Gynecology at Silverado, Napa. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

June 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 35 hrs. $1,200.

June 28-29—**5th Annual Trauma Seminar.** DREW at Disneyland Hotel, Anaheim. Thursday-Friday. 16 hrs. $175.

(Continued on Page 893)

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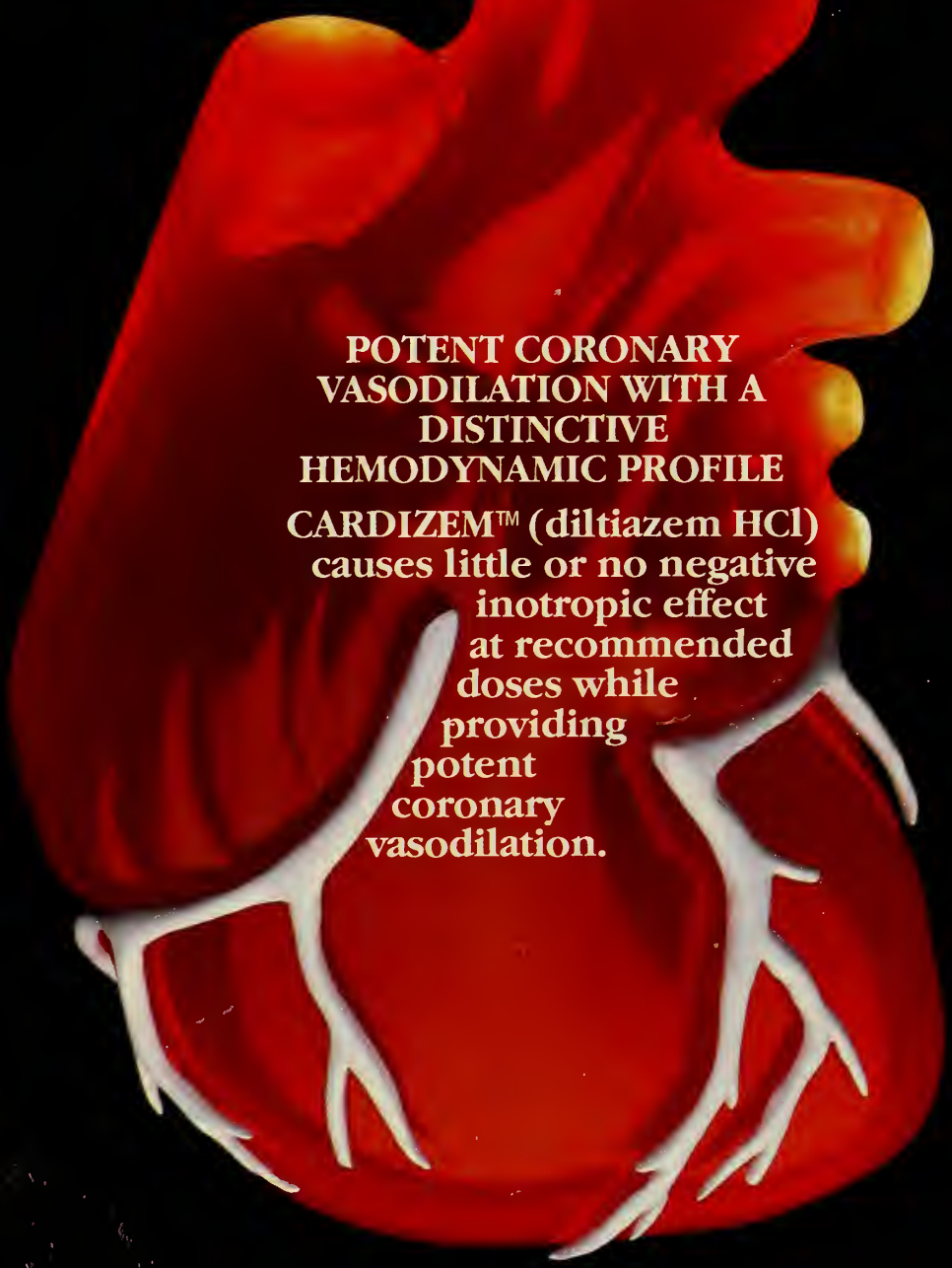
from
Marion Laboratories



POTENT CORONARY VASODILATION WITH A DISTINCTIVE HEMODYNAMIC PROFILE

CARDIZEM™ (diltiazem HCl) causes little or no negative inotropic effect at recommended doses while providing potent coronary vasodilation.

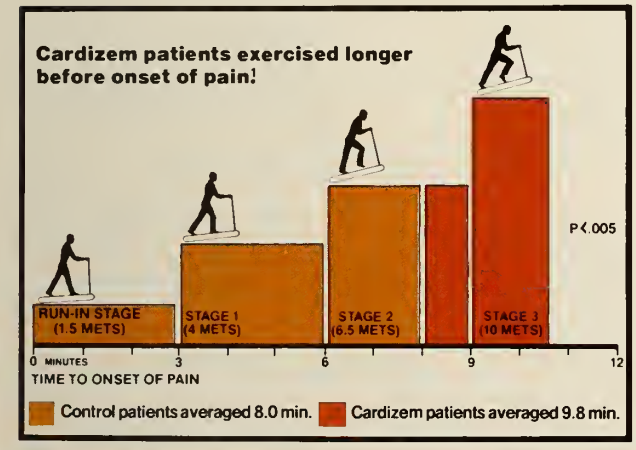
Please see full prescribing information on last page of this ad.

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY* WITH A LOW INCIDENCE OF SIDE EFFECTS

Calcium channel blockade with CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

CARDIZEM™ (diltiazem HCl) ALLOWS PATIENTS TO SIGNIFICANTLY PROLONG EXERCISE TOLERANCE, EVEN IN DEMANDING BRUCE PROTOCOL EXERCISE TESTS[1] (n = 15)†



This study is of special significance because patients not only exercised longer but *to the next higher stage* in the Bruce protocol.

A Bruce protocol with a run-in stage was used for all tests. Each stage lasts three minutes.

In other studies, Cardizem produced 41% to 68% reduction of Prinzmetal's variant angina attacks[2]

†This study is a report from one center in a multicenter study.

Therapy with Cardizem produced a low incidence of side effects.

In placebo-controlled trials (222 patients) conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with Cardizem in 959 patients in controlled and uncontrolled U.S. trials have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

Other reactions reported infrequently (less than 1%) are listed in full prescribing information on adjacent page.

Please see adjacent page for full prescribing information.

References:

1. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl): 234-238, 1980.
2. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.

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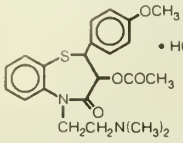
PROFESSIONAL USE INFORMATION

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (four of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem tid of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to the drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY MISSOURI 64137

3/83

A Near-Spotless Record.

Other OCs claim it. We show it.[1*]

In clinical trials, Lo/Ovral was practically perfect in holding spotting and breakthrough bleeding to a minimum.[†]

	SPOTTING	BREAKTHROUGH BLEEDING
Cycle 1	10.6%	8.8%
Cycle 3	6.3%	3.3%
Total Cycles[‡]	4.2%	2.9%

Lo/Ovral® offers less breakthrough bleeding and spotting, along with high contraceptive efficacy, at a low dose—just 30 mcg ethinyl estradiol and 0.3 mg norgestrel.

LOW DOSE

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth.

1 Dickey RP Managing Contraceptive Pill Patients, 3rd ed., Duront, Oklahoma, Creative Informatics, Inc., 1983

*Rates are derived from separate studies from different investigators in several population groups and cannot be compared precisely

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives

‡Data on file for 22,489 total cycles, Wyeth Laboratories **See important information on following page**

IN BRIEF:

Indications and Usage -LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions:

1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding.
7. Known or suspected pregnancy (see Warning No. 5).
8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia, papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind.

In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests.

As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin(TBG)leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome; headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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(Continued from Page 885)

July 7-14—**Cardiovascular Medicine and Surgery and Critical Care Medicine.** See Cardiology, July 7-14.

August 13-17—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 17-21—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

September 20-22—**Microsurgery: An Introduction to Microtechnique for Small Artery and Nerve Repair.** American Academy of Orthopaedic Surgeons at San Diego. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

October 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

October 9-14—**American Society of Plastic and Reconstructive Surgeons Inc., American Society of Maxillofacial Surgeons Inc. and Plastic Surgery Educational Foundation Meeting** at Las Vegas. Tuesday-Sunday. Contact: ASPRS-PSEF, Exec. Office, 233 N. Michigan Ave., Ste. 1900, Chicago 60601.

October 10-14—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. 34 hrs. $1,200.

October 11-13—**Controversies in Urology.** American Urological Association at San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, PO Box 25147, Houston, TX 77265. (713) 799-6070.

October 14-18—**Western Orthopedic Association Meeting** at San Diego. Sunday-Thursday. Contact: WOA, 1970 Broadway, Ste. 1235, Oakland 94612. (415) 893-1257.

October 17-21—**Advanced Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. $1,200.

October 21-26—**American College of Surgeons Meeting** at San Francisco. Sunday-Friday. Contact: ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 27—**Lumbar Spine and Pelvis.** UCSD at Hotel del Coronado, Coronado. Saturday.

October 28-November 9—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 29-November 3—**Basic Microsurgery Training Workshop.** UCSD at Surgery Research Lab, University Hospital, San Diego. Monday-Friday. $1,200.

OF INTEREST TO ALL PHYSICIANS

June 17-23—**UCI Family Practice Refresher Course.** UCI and Memorial Medical Center of Long Beach at Grand Hotel, Anaheim. One week. Contact: MMCLB, 2801 Atlantic Ave., Long Beach 90801. (714) 595-3811.

June 18—**Transplant '84.** UCSF. Monday.

June 18-20—**Aluminum-Related Disease: Features, Pathogenesis, Recognition and Treatment and Prevention.** UCLA at The Newporter, Newport Beach. Monday-Wednesday. 20 hrs. $150.

June 18-23—**UCI Family Practice Refresher Course.** UCI at Disneyland Hotel. Monday-Saturday.

June 20-24—**Golden State Medical Association Annual Scientific Session** at Hawaiian Regent Hotel, Oahu. Wednesday-Sunday. Contact: Lillian Fortier, GMSA, PO Box 2151 Station A, Berkeley 94702.

June 21-23—**1st Annual Superficial Anatomy and Cutaneous Surgery for Dermatologists: 1984.** UCSD. Thursday-Saturday. 22.5 hrs. $500.

(Continued on Page 992)

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Potassium-Sparing

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

In Hypertension*...When You Need to Conserve K^+

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for Institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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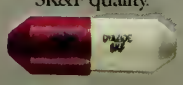

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Mycoplasma pneumoniae Pneumonia

Experience at a Referral Center

DOUGLAS H. LINZ, MD; SUSAN W. TOLLE, MD, *and* DIANE L. ELLIOT, MD, *Portland*

Mycoplasma pneumoniae *pneumonia is usually a benign illness, and respiratory complications and extrapulmonary manifestations occur rarely. In this series, patients admitted to a referral hospital with this disorder had unusual symptoms, signs and findings on chest roentgenograms and laboratory studies. Pneumonia was often severe and extrapulmonary manifestations were frequent, resulting in prolonged hospital stays and illnesses. Although this extreme end of the spectrum of disease caused by* M pneumoniae *is not representative of this type of pneumonia as seen in outpatients, it is important to realize that patients admitted to hospital with severe, complicated pneumonia frequently have unusual manifestations of a common disease.*

(Linz DH, Tolle SW, Elliot DL: *Mycoplasma pneumoniae* pneumonia—Experience at a referral center. West J Med 1984 Jun; 140:895-900)

Mycoplasma pneumoniae pneumonia is usually an acute, self-limited, febrile illness associated with nonproductive cough and rarely requires admission to hospital.[1] Patients with *M pneumoniae* pneumonia who require hospital care are more likely to have a disorder similar to bacterial pneumonia with high fever, pleuritic chest pain and purulent sputum. Leukocytosis and a left-shifted differential, chest roentgenographic findings of lobar consolidation and a clinical course characterized by respiratory insufficiency and protean nonpulmonary manifestations may be present.[2]

The diverse extrapulmonary manifestations of *M pneumoniae* pneumonia[2-4] include hemolytic anemia, thrombocytopenic purpura, disseminated intravascular coagulation, pancreatitis, gastroenteritis, hepatitis, monoarticular or polyarticular arthritis, myopericarditis, erythema multiforme major and other skin rashes, meningitis, meningoencephalitis, peripheral or cranial neuropathy, cerebellar ataxia, transverse myelitis, psychosis, splenomegaly and generalized lymphadenopathy. Nonpneumonitic respiratory tract manifestations include otitis, bronchitis, pleural effusion, lung abscess and exacerbation of asthma and chronic obstructive pulmonary disease. The extrapulmonary manifestations are rare, with cases described as single reports or small series.

This is the first article to review the clinical manifestations of this disorder in patients admitted to hospital at a referral center. The clinical presentation and course of illness were distinctive in many patients, and a high incidence of serious and rare complications was observed.

Patients and Methods

All available charts were reviewed of patients admitted to the University of Michigan Hospital (Ann Arbor) between January 1971 and December 1979 with either *M pneumoniae* (MP) isolated from sputum or a discharge diagnosis of *M pneumoniae* pneumonia or atypical pneumonia. The search included all patients with nonbacterial pneumonia, including those with viral pneumonia. Pneumonias proved to be due to other infectious agents or failing to meet diagnostic criteria for *M pneumoniae* pneumonia were excluded. The remaining cases were grouped based on diagnostic certainty as either probable or definite *M pneumoniae* pneumonia.

A definite diagnosis was made when the organism was isolated in culture from sputum specimens or when there was a fourfold rise in MP complement-fixation

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ABBREVIATIONS USED IN TEXT
CNS = central nervous system
CSF = cerebrospinal fluid
MP = *Mycoplasma pneumoniae*
PPD = purified protein derivative

antibody titers. Cases with a single complement fixation titer of 1:64 or greater and cold agglutinin titer 1:64 or more or with a fourfold rise in cold agglutinin titer, with maximum titer 1:64 or more were listed as probable *M pneumoniae* pneumonia. Cold agglutinin and complement-fixation studies were done in the usual manner, and MP culture and identification were according to the technique of Chanock and co-workers[5] with minor modifications.

Data obtained on each patient included age and sex, initial symptoms and signs, laboratory data, treatment, hospital course and referral status. Postdischarge course was noted when available.

Results

Of 107 charts identified, 102 were reviewed. Fifty cases of atypical pneumonia were shown to be due to other organisms, and 27 cases with a discharge diagnosis of *M pneumoniae* pneumonia failed to meet diagnostic criteria. These 27 patients were all empirically treated for this disorder and discharged without obtaining convalescent cold agglutinin or MP complement-fixation titers. A total of 25 cases fulfilled criteria for *M pneumoniae* pneumonia, 16 definite and 9 probable. The organism was identified from expectorated sputum specimens from 13 of 16 patients with definite *M pneumoniae* pneumonia. Four of nine patients with probable *M pneumoniae* pneumonia had a fourfold rise in cold agglutinin titer as the only confirmatory test while complement-fixation and MP cultures were not done.

Epidemiology

Infection was most common during fall and winter, occurring in young adults with a mean age of 29 years (range 6 to 69 years). Eleven patients were male and 14 female. Six patients had a history of exposure from family members who had either symptoms of respiratory tract infection or proved pneumonia.

Symptoms and Signs

Symptoms and signs noted at any time during the course of infection are listed according to frequency in Tables 1 and 2. Hacking cough with minimal sputum production was present in all patients, and in a third purulent sputum developed within a week of the onset of symptoms. In all, 21 (84%) patients had temperatures of 39°C (102°F) or higher, yet rigors occurred in only three patients. Only a quarter (six) complained of headache. Of the 25 patients, 7 (28%) had pleuritic chest pain, and this was the sole initial symptom in two patients with definite *M pneumoniae* pneumonia. Symptom duration before hospital admission varied from 1 to 34 days, with a mean of 13 days. Rales were heard on initial or subsequent examination in about three quarters of patients. Evidence of consolidation (8 [32%]) or bronchospasm (10 [40%]) was occasionally present without rales. Only five patients had normal lungs on examination.

Laboratory Evaluation

Chest roentgenograms showed infiltrates in all patients, in 14 (56%) involving a single lobe. Five patients (20%) had involvement limited to the upper lobes, suggesting possible tuberculosis. Three patients had diffuse infiltrates and five had pleural effusions. Three effusions were either moderate or large.

Total and differential leukocyte counts were normal (4,000 to 10,000 per μl) in only ten (40%) patients; six (24%) had a normal total leukocyte count but a left-shifted differential (more than 5% band forms), and three patients (12%) had leukocyte counts greater than 15,000 per μl. Sputum Gram's stain and routine bacterial cultures were done in 24 patients and showed mixed oral flora except in two cases of bacterial coinfection.

Unusual Pulmonary Manifestations

Many patients in this series had unusual pulmonary manifestations of *M pneumoniae* pneumonia. Two pa-

TABLE 1.—*Frequency of Symptoms of* Mycoplasma pneumoniae *Pneumonia in 25 Patients at University of Michigan Hospital (Ann Arbor)*

Symptoms	*Patients* Total N=25 Percent	Definite N=16 Percent	Probable N=9 Percent
Very Common (50% or more)			
Cough	100	100	100
Fever >39°C (102°F)	84	81	89
Malaise	76	75	78
Chills	64	69	56
Common (20% to 50%)			
Purulent sputum	36	38	33
Arthralgias and myalgias	36	38	33
Pleuritic chest pain	28	19	44
Headache	24	19	33
Sore throat	24	19	33
Anorexia	24	13	44
Uncommon			
Nausea and vomiting	8	13	..
Ear discomfort	8	13	..
Hemoptysis	8	13	..
Diarrhea	8	..	22
Rhinorrhea	4	6	..

TABLE 2.—*Frequency of Signs of* Mycoplasma pneumoniae *Pneumonia in 25 Patients at University of Michigan Hospital (Ann Arbor)*

Signs	*Patients* Total N=25 Percent	Definite N=16 Percent	Probable N=9 Percent
Rales	72	63	89
Wheezes	40	38	44
Dullness or egophony	32	31	33
Pharyngeal erythema	16	19	11
Cervical adenopathy	16	25	..
Rash	8	6	11
Myringitis	4	6	..
Normal lung on examination	20	25	11

tients with a definite diagnosis and no evidence of superinfection required intensive care because of diffuse pneumonitis with pronounced hypoxemia and cyanosis. Although mechanical ventilation was not required in either case, the admitting physicians were rightfully concerned about the possible development of the adult respiratory distress syndrome. Both patients recovered promptly in response to treatment with erythromycin.

Two further cases illustrate the varied pulmonary presentation of *M pneumoniae* pneumonia in a referral hospital setting. A six-year-old girl whose case was reported elsewhere[6] had a chronic illness of one month's duration and persistent right upper lobe consolidation simulating tuberculosis on roentgenogram. She had persistent cough, spiking fever, myalgias, arthralgias and malaise and on physical examination had a blood pressure of 102/64 mm of mercury, pulse rate 140 per minute, respirations 52 and a temperature of 38°C (99.6°F). Bilateral crackles and wheezes and dullness to percussion at the left base were present on lung examination, and she had bilateral serous otitis media. The hemoglobin was 8.6 grams per dl and leukocyte count 15,050 per μl, with 65% segmented neutrophils, 16% band forms and 13% lymphocytes (all atypical).* Corrected reticulocyte count was 5.0%. Sputum bacterial culture grew oral flora, and chest roentgenogram showed left upper lobe consolidation and left lower and right upper lobe infiltrates. Serial cold agglutinin titers were 1:64 and 1:1,024, and MP complement-fixation titers were both 1:512. A Coombs' test was strongly positive with anti-I specificity. Fungal and tuberculosis smears and cultures of expectorated sputum and brushing and washing specimens obtained at two bronchoscopies were negative. An open-lung biopsy was done. Pathologic examination of the specimen showed caseating granulomas and cultures grew *M pneumoniae*. She was treated for pulmonary tuberculosis and her condition gradually improved over a further five weeks in hospital. Chest roentgenograms showed persistent volume loss in the left upper lobe at six months and three years.

Chronic atelectatic upper lobe disease mimicking pulmonary tuberculosis is rare in cases of *M pneumoniae* pneumonia and coinfection with *Mycobacterium tuberculosis* remains possible despite negative cultures.

A 32-year-old woman, three months' postpartum after normal gestation and delivery, was admitted with right posterior pleuritic chest pain and nonproductive cough of four weeks' duration. Chest roentgenogram done three weeks earlier had shown no abnormalities. Six days before admission, exudative pharyngitis developed and she was treated with erythromycin; four days later she had left-sided pleuritic chest pain. Blood pressure was 110/70 mm of mercury, pulse rate 74 per minute, respirations 18 and temperature 37°C (98.6°F). A pleural friction rub over the posterior right hemithorax was the only abnormal physical finding. Her hemoglobin was 11.7 grams per dl and a leukocyte count was 7,900 per μl, with 51% segmented neutrophils, 21% band forms and 24% lymphocytes (some atypical). Chest roentgenogram showed a right upper lobe, pleural-based infiltrate, and ventilation-perfusion lung scan showed no abnormalities. Routine sputum culture grew oral flora, and MP was identified in a sputum specimen two weeks after admission. Purified protein derivative (PPD) skin test and sputum smears and cultures for *M tuberculosis* and fungi were negative. She was discharged improved on a regimen of erythromycin, and chest roentgenogram a week later showed some resolution of the infiltrate. On follow-up visit a month later, her chest pain had diminished, a friction rub was still audible and chest roentgenogram showed further resolution.

*Only significant values are given

TABLE 3.—*Manifestations of* Mycoplasma pneumoniae *Pneumonia in 25 Patients at University of Michigan Hospital (Ann Arbor)*

Manifestations	*Patients*		
	Total N=25 Percent	*Definite N=16 Percent*	*Probable N=9 Percent*
*Nonpneumonitic Respiratory Tract**	36	38	33
Asthma or bronchitis	16	12	22
Pleural effusion			
Moderate or large	12	12	11
Bacterial bronchitis	4	6	0
Bacterial pneumonia	4	6	0
*Extrapulmonary**	40	44	33
Hematologic			
Hemolytic anemia, anti-I	24	25	22
Dermatologic			
Stevens-Johnson syndrome	4	0	11
Neurologic	12	12	11
Meningitis	4	6	0
Meningoencephalitis	4	6	0
Encephalitis	4	0	11
Myopericarditis	4	6	0

*Patients with more than one nonpneumonitic respiratory tract or extrapulmonary manifestation were counted once.

Pleuritic chest pain simulating pulmonary embolization is an unusual presenting manifestation of *M pneumoniae* pneumonia but occurred in seven patients in this series.

Nonpneumonitic Respiratory Tract Manifestations

Nine patients (36%) had nonpneumonitic respiratory tract manifestations of *M pneumoniae* pneumonia (Table 3). Exacerbation of asthma or chronic bronchitis occurred in four patients. *Klebsiella pneumoniae* superinfections developed in two patients who had culture-proved *M pneumoniae* pneumonia, one of whom required intensive care.

Extrapulmonary Manifestations

Extrapulmonary manifestations of *M pneumoniae* in this series included hematologic, dermatologic, neurologic and cardiac diseases (Table 3). The most frequent were hematologic. Six patients, four with definite and two with probable *M pneumoniae* pneumonia, had hemolytic anemia associated with a positive direct Coombs' reaction and anti-I antibodies. In four, the anemia was mild to moderate in severity with hemo-

globins ranging from 9 to 11 grams per dl, while two others had severe anemia. One of these, a 29-year-old woman, was admitted with 2½ weeks of nonproductive cough and fever to 39.8°C (103.6°F), a ten-day history of pleuritic chest pain with shortness of breath and three days of jaundice and tea-colored urine. She was pale and icteric; her blood pressure was 118/56 mm of mercury, pulse rate 100 per minute, respirations 16 and temperature 37°C (98.6°F). Bilateral basilar wheezes and rales and a left retinal hemorrhage were present. Hemoglobin was 5.7 grams per dl, hematocrit 16% and leukocyte count was 59,700 per μl, with 57% segmented neutrophils, 15% band forms, 9% metamyelocytes, 6% myelocytes and 1% myeloblasts; there were 14% nucleated erythrocytes. Corrected reticulocyte count was 48.3% and serum bilirubin level was 4.0 mg per dl. A chest roentgenogram showed bilateral diffuse reticulonodular infiltrates. Serial titers for MP complement fixation were 1:32 and 1:64, and cold agglutinin titers were 1:1,280 and 1:512. Sputum was not obtainable. A Coombs' test was strongly positive with anti-I specificity, and bone marrow aspiration and biopsy specimen showed no abnormalities except for erythroid hyperplasia. She was treated with an oral regimen of erythromycin, prednisone (60 mg a day), ferrous sulfate and folic acid. Her cough and fever resolved over the next two days, and a chest roentgenogram showed normal results 12 days later. The prednisone dosage was tapered over three months as her cold agglutinin titers declined. She remained well over a two-year follow-up.

Hemolytic anemia of this severity is an uncommon manifestation of *M pneumoniae* pneumonia, as is leukocytosis of this magnitude. The coexistence of pneumonia and unexplained anemia should raise the possibility of this disorder.

Dermatologic manifestations included one case of Stevens-Johnson syndrome. A 16-year-old man was transferred for treatment of pneumonia and Stevens-Johnson syndrome. Ten days before admission, nonproductive cough, sore throat and prostration developed. Four days later he was seen in the emergency room of another hospital febrile to 41.3°C (106.4°F) and he had a right lower lobe infiltrate on chest roentgenogram. He was admitted and treated with a cooling blanket, procaine penicillin given intramuscularly and ampicillin by mouth. The next day, he had photophobia and a blistering eruption over his entire body, including the buccal mucosa and genitalia; he was transferred to the University of Michigan Hospital. On arrival, he appeared acutely ill with a blood pressure of 110/60 mm of mercury, pulse rate 120 per minute, respiratory rate 22 and temperature 39°C (102.4°F). Extensive oral and perineal ulcerations and multiple bullous and targetoid lesions involving the extremities, face and trunk were present. The hemoglobin was 12.9 grams per dl, hematocrit 37.7% and leukocyte count 5,700 per μl with 18% segmented neutrophils, 47% band forms and 1% myelocytes. Pronounced rouleaux formation was noted. A sputum culture grew oral flora, and a chest roentgenogram showed a resolving right lower lobe infiltrate. Acute and convalescent titers for MP complement fixation were positive at 1:512, and an acute cold agglutinin titer was 1:640. Coombs' antibody studies were not done. Monospot, hepatitis B surface antigen and VDRL tests were negative. The patient had received penicillin in the past without adverse effects. He received erythromycin, prednisone and topical and ophthalmic corticosteroids. Chest roentgenogram findings returned to normal three days after admission, and his skin rash resolved over three weeks.

Dermatologic manifestations of *M pneumoniae* infection include maculopapular exanthems, urticaria and Stevens-Johnson syndrome.

Three patients had neurologic manifestations of *M pneumoniae* pneumonia: encephalitis, meningitis and meningoencephalitis. Of these, the case of meningoencephalitis was unusual in that neurologic symptoms antedated pulmonary symptoms. A previously healthy 24-year-old man was admitted because of headache and fever for nine days. Over four days, back pain, tinnitus, progressive gait instability and mental state deterioration had developed. On physicial examination he had a temperature of 38.8°C (101.8°F), a positive Romberg sign and right lateral nystagmus. Chest roentgenogram showed no abnormalities. A cerebrospinal fluid (CSF) specimen showed a mononuclear cell pleocytosis. Computed tomographic brain scan was normal, and electroencephalogram showed diffuse slowing of the background rhythm without focal changes or paroxysms. Five days later cough developed and chest roentgenogram confirmed the physical findings of right lower lobe pneumonia with a moderate pleural effusion. A sputum culture was positive for *M pneumoniae*. Routine bacterial, fungal and mycobacterial cultures of sputum and CSF specimens were negative. A diagnostic thoracentesis showed an exudative effusion with 8,350 leukocytes per μl, with 40% segmented neutrophils, 12% lymphocytes and 40% mesothelial cells. He was treated with intravenous administration of erythromycin and later erythromycin by mouth, with gradual resolution of his fever and cough. Chest roentgenogram one month after admission showed no abnormalities. During two years' observation, the patient had continued intellectual impairment, depression, memory loss and cerebellar dysfunction resulting from his meningoencephalitis.

Neurologic syndromes are the most frequently reported extrapulmonary manifestations of *M pneumoniae* pneumonia, with meningitis being the most common.[4] Patients with meningitis typically recover without neurologic residue, whereas those with encephalitis may suffer permanent deficits.

Cardiac manifestations were limited to a single case of acute myopericarditis. A 31-year-old woman had left pleuritic chest and shoulder pain, fever to 39°C (102.4°F) and a nonproductive cough of two weeks' duration. She had bilateral large pleural effusions and a left lingular infiltrate on chest roentgenogram, diffuse ST-segment elevation with T-wave inversion on elec-

trocardiogram and a moderate to large pericardial effusion on echocardiogram. MP was isolated from sputum and she had anti-I, Coombs'-positive hemolytic anemia with a hemoglobin of 9.7 grams per dl. Sputum routine bacterial culture grew normal flora, a PPD skin test was negative and results of thoracentesis showed an exudative effusion with 1,320 leukocytes per μl, 65% segmented neutrophils, 7% lymphocytes and 18% histiocytes and mesothelial cells. The specimen from a Cope needle pleural biopsy showed slight inflammation. Routine bacterial, fungal and mycobacterial cultures of pleural biopsy, pleural fluid and sputum specimens were negative. She became asymptomatic over ten days on a regimen of erythromycin by mouth and remained well during the subsequent three years.

Myopericarditis associated with *M pneumoniae* pneumonia is uncommon. Chronic cardiomyopathy may ensue despite appropriate antibiotic therapy, though most patients recover without permanent disability.

Nonpneumonitic respiratory tract and extrapulmonary manifestations of *M pneumoniae* infection were common in this series of in-hospital patients. If minor manifestations including unspecified anemia, small pleural effusion, skin rash, urticaria and otitis are eliminated from analysis, 6 of 16 patients (38%) with definite *M pneumoniae* pneumonia had nonpneumonitic respiratory manifestations and 7 (44%) extrapulmonary manifestations. Three of nine patients (33%) with probable *M pneumoniae* pneumonia had nonpneumonitic respiratory tract manifestations, and three had extrapulmonary manifestations.

Therapy and Follow-up

Erythromycin or tetracycline therapy was given to all but four patients in this series, and many patients responded within two days with defervescence and decreased severity of cough. However, time to relief of symptoms and resolution of roentgenographic abnormalities was often prolonged. In 7 of 14 patients seen as outpatients after discharge, symptoms and chest roentgenographic findings had completely or nearly totally resolved within a month. Two asymptomatic patients had residual radiographic abnormalities two months and three months after discharge. Four patients had persistent cough, wheezing or pleuritic chest pain and unresolving infiltrates on chest x-ray film when seen 5 to 11 weeks after discharge. One patient had normal findings on a chest roentgenogram but persistent pleuritic chest pain six weeks after discharge.

Length of Hospital Stay

The stay in hospital was often brief, with ten (40%) patients in hospital for six days or less. Twelve (48%) patients were seen in referral from community hospitals, and the rest were seen initially at the University of Michigan. Of the patients seen initially at the University of Michigan, 9 (69%) were in hospital for less than a week, whereas 10 (83%) of those referred from community hospitals remained in hospital for one week or longer. The average hospital stay was 16.7 days, with a range of 3 to 60 days.

Discussion

M pneumoniae pneumonia is a common respiratory tract illness and accounts for about 20% of cases of community-acquired pneumonia.[7] It is usually an outpatient disease. The course of this disease was studied over an eight-year period in a large prepaid medical care group in Seattle.[1] Only 2% of 439 children and 6% of 173 adults with *M pneumoniae* pneumonia required admission to hospital. Statements regarding the usual clinical, laboratory and roentgenographic findings and the incidence of extrapulmonary manifestations of *M pneumoniae* pneumonia largely reflect experience with outpatients.[2,4]

A limited number of reported series are of patients admitted to hospital with *M pneumoniae* pneumonia. A prospective study of patients in hospital with acute respiratory tract infections in Sweden showed that 24% of patients with pneumonia had evidence of *M pneumoniae* pneumonia.[8] Serious complications occurred in only 5 of 90 in-hospital patients and included erythema nodosum in two, meningoencephalitis in one and superimposed *Staphylococcus aureus* septicemia in two. Of 44 children admitted to hospital during an 18-month epidemic of *M pneumoniae* pneumonia in Bristol, England, six had seven extrapulmonary complications including two cases of meningitis, four cases of Stevens-Johnson syndrome and one case of acute hemolytic anemia.[9] Ponka,[4] reviewing the case records of patients admitted to public hospitals in Helsinki over a seven-year period, looked specifically for central nervous system (CNS) manifestations, carditis and arthritis and found incidences of 4.8% (27 of 560 patients), 4.5% (25 of 560 patients) and 0.9% (11 of 1,259 patients), respectively. Two other series have shown similar incidences of CNS manifestations and carditis in in-hospital patients.[10,11] Thus, as would be expected, patients requiring hospital care are more likely to have unusual manifestations.

The findings in this series of patients admitted to a referral center emphasize this trend. Patients—and particularly those transferred from other hospitals—were older and presented with unusual symptoms, signs and roentgenographic and laboratory findings. Their pneumonias tended to be more severe and extrapulmonary manifestations were frequent. The relatively small number of patients in this study likely reflects the fact that hospital treatment for *M pneumoniae* pneumonia is uncommon and less frequently required in younger patients.[1] The mean age of patients in this series was 29 years, the same as that in another series of 90 patients requiring hospital care.[8]

Unusual symptoms and signs in this series included a high incidence of pleuritic chest pain, occurring in nearly a third of patients, and a low incidence of headache occurring in less than a fourth of the patients. While 18 (72%) patients had rales, dullness to chest

percussion or egophony was noted in 8 (32%), and wheezes, not specifically mentioned in other series, were present in 10 (40%).

Chest roentgenographic findings in this patient group were unusual in that lower lobe involvement was less common, and large pleural effusions on standard projections were more common than previously reported.[12,13] Three effusions were read as either moderate or large, and infiltrates limited to the upper lobes were a surprisingly frequent finding.

Leukocytosis and left-shifted differential leukocyte counts were frequent. Whereas 16 (64%) of the patients in this series had a normal leukocyte count, 6 of those had a left-shifted differential leukocyte count. Thus, most patients had either leukocytosis or significantly left-shifted differential leukocyte counts.

The unusually severe clinical course of *M pneumoniae* pneumonia in this series of patients is reflected by the necessity for intensive respiratory care in three patients, with mechanical ventilatory support in two. In addition, hospital stays were often prolonged and symptoms unusually persistent. Patients were in hospital for an average of 2½ weeks. At five or more weeks following hospital discharge, 9 of 14 (64%) patients had persistent symptoms and 6 (43%) had residual chest roentgenographic abnormalities.

The frequencies with which nonpneumonitic respiratory tract and major extrapulmonary manifestations of *M pneumoniae* pneumonia occurred in this series of patients were 36% and 40%, respectively. Initial diagnostic considerations included adult respiratory distress syndrome of unknown cause, tuberculosis, leukemia and pulmonary embolism. Perhaps most striking was the fact that 6 (24%) patients had significant anemia associated with a positive direct Coombs' reaction and the demonstration of anti-I antibodies. Antibiotic therapy did not appear to affect the course of the extrapulmonary manifestations.

Several factors contributed to the high incidence of severe pneumonia and nonpneumonitic respiratory tract and extrapulmonary manifestations of *M pneumoniae* pneumonia in this series. First, 12 (48%) patients were transferred from outlying hospitals. These referral patients were unusually ill, accounting for 71% of hospital stays of one week or longer. Second, diagnostic studies, including acute and convalescent cold agglutinin titers, MP complement-fixation titers and MP isolation and identification techniques, require a minimum of two weeks for diagnostic confirmation. Patients with an uncomplicated illness of short duration were likely to have been excluded because diagnostic studies were never done, thus skewing this series to patients with prolonged and severe illness.

Alternatively, by including four patients with significant elevation of cold agglutinins as the only confirmatory diagnostic study, results may have been skewed in the opposite direction, as none of them had extrapulmonary manifestations. Although significantly elevated cold agglutinin titers are found in a number of illnesses including viral respiratory tract infections and legionnaires' disease, it is reasonable to consider that such patients probably have *M pneumoniae* pneumonia. In fact, 72% to 92% of patients with pneumonia in whom significant titers of cold agglutinins develop also acquire titers of specific MP antibodies.[14]

It is not our intent to alter readers' perceptions regarding the usual manifestations and appropriate management of *M pneumoniae* pneumonia as seen in an outpatient setting. The vast majority of patients who have this disorder are young and have uncomplicated illness responsive to treatment with oral erythromycin or tetracycline. Several important conclusions can be drawn from the findings in this series of patients with *M pneumoniae* pneumonia admitted to a referral center. Such patients are likely comparable to the sicker patients seen at a community hospital.

Patients admitted to hospital with *M pneumoniae* pneumonia are likely to have severe pneumonia with unusual symptoms, signs, roentgenographic findings and laboratory values. They frequently have nonpneumonitic respiratory tract and extrapulmonary manifestations that may have higher morbidity than the pneumonia. The diagnosis of *M pneumoniae* pneumonia should be strongly considered and diagnostic studies done in patients presenting with pneumonia and evidence of other organ system involvement.

None of the signs and symptoms of this disease are pathognomonic. However, in a case of an otherwise healthy patient who has pneumonia and anemia, Coombs' tests should be done. Coombs' positivity associated with anti-I antibodies should strongly suggest the diagnosis, and empiric appropriate antibiotic therapy should be instituted even before diagnostic confirmation.

With the recent addition of legionnaires' disease and its closely related family of diseases to the differential diagnosis of atypical pneumonia, recognition of the complete spectrum of illness associated with *M pneumoniae* pneumonia is timely.

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Cysticercosis Update

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Already the most common brain parasite disease, cysticercosis has been increasingly seen throughout the American Southwest. Symptoms arise from infection with larvae of Taenia solium, *the pork tapeworm. Seizures, hydrocephalus, focal deficits and chronic meningitis most commonly result. Cerebrospinal fluid eosinophilia, serology by indirect hemagglutination and computed tomography are helpful adjuncts to diagnosis. New evidence suggests that selective immunosuppression is important for the parasites' survival and that cyst death permits renewed host immunity, which may actually precipitate an acute neurologic presentation. New larvicides, including praziquantel, are being tested in humans; caution is indicated in assessing these drugs because of the acute worsening associated with cyst death. Conventional therapy includes anticonvulsants, steroids or ventricular drainage as needed. Prevention remains the best management. Person-to-person transmission within the United States has recently been documented and merits public health scrutiny.*

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Cysticercosis has long been the most important central nervous system parasitic disease in the Third World but is only now achieving significant impact in the United States. In the past decade, hospitals throughout the Southwest have seen increasing numbers of cases, as attested to by several recent clinical series.[1-6] Immigration from Mexico and other endemic areas accounts for the rising incidence of cysticercosis in California and other states. In 1980 there were 4.5 million Mexicans and Chicanos living in California. Nationally, the Mexican-descended population increased from 4.5 million in 1970 to 8.7 million in 1980, with a trend towards wider distribution across the country.[7] There is now evidence of transmission of the disease between persons living within the United States.[2,8] Clinical findings in cases of cysticercosis and its laboratory diagnosis are detailed in recent reports[1,2]; this review focuses on new concepts in pathogenesis and implications for therapy.

Cysticercosis is the systemic infection with the larval stage of *Taenia solium*, the pork tapeworm. The normal life cycle of *T solium* alternates between human tapeworm infestation and swine cysticercosis. Tapeworm eggs passed in infected human feces are eaten by pigs. In the pig intestine the eggs release embryos that burrow into the mucosal wall and enter the bloodstream, ending as encysted larvae (cysticerci) in multiple organs, chiefly muscle and brain. When humans eat poorly cooked, infected pork, the larvae attach in the gut lumen and become adult tapeworms, thus completing the cycle. Human cysticercosis results when humans become infected with the eggs through fecal-oral contamination or an equivalent mechanism (Figure 1).

Central nervous system lesions usually occur in the cerebral parenchyma, subarachnoid cisterns and ventricles. The larvae typically live for several years, then die, often with a dense local inflammatory response. Onset or exacerbation of symptoms may coincide with cyst death.[9] With time, the dead cysts may calcify.

Clinical manifestations depend on where the cysticerci become established. Muscle lesions usually cause no symptoms, though a painful myositis can result. Cortical lesions may produce seizures or focal neurologic deficits, or both. Ventricular lesions result in a noncommunicating hydrocephalus, occasionally with a ball-valve mechanism causing syncope due to sudden complete blockage.[2] Cisternal lesions cause a chemical meningitis (which may present with an acute, subacute or chronic course), communicating hydrocephalus, cranial nerve palsies or dementia. True strokes may re-

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sult if this inflammation thromboses a cerebral vessel, though sudden focal deficits may also result from strictly parenchymal cysts, presumably without a vascular basis. Rarely, cyst lesions may mimic numerous other syndromes.[1]

Screening laboratory studies are not helpful. Examination of a cerebrospinal fluid specimen may show any pattern, mimicking a bacterial or an aseptic meningitis or even appearing normal with some ventricular or deep parenchymal lesions. Findings such as increased γ-globulin levels can mimic multiple sclerosis or any chronic infection. Cerebrospinal fluid eosinophilia may be found with a Wright's or an eosinophil stain (*not* with routine differential by a counting chamber), which is highly suggestive but not diagnostic.[10] Serology by indirect hemagglutination may be carried out on serum or cerebrospinal fluid specimens through the Centers for Disease Control. It is positive in 60% to 80% of all patients,[2] with fewer false-negatives in the meningitic or acute parenchymal forms and almost no false-positives except in other parasitic infections,[11] especially echinococcosis.[12] Serology done on serum specimens appears more sensitive than that on cerebrospinal fluid. Other serologic studies are under investigation.[13]

Computed tomographic (CT) findings have been well documented.[14-16] Depending on the state of infection, parenchymal lesions may be invisible, cystic, hypodense (with or without contrast enhancement) or calcified. Ventricular lesions may cause focal hydrocephalus and often require CT ventriculography for precise delineation.[17] Ventricular cysts may move if a patient changes position. Subarachnoid lesions may be associated with extra-axial cysts, basilar cisternal contrast enhancement or, most commonly, hydrocephalus. Other radiologic studies including plain films of skull or soft tissues, angiography and so forth are usually not helpful.

Currently, the diagnosis rests on clinical criteria bolstered by epidemiologic (Mexican or other endemic exposure) and laboratory (serology, CT scan or biopsy) findings. No single test can either "rule out" the diagnosis or completely exclude other diseases.

Conventional therapy is symptomatic, including anticonvulsants, steroids or ventriculoperitoneal shunting as needed. Surgical excision is rarely required. The best management is prevention by adequate sanitation and by vigorously searching for and treating tapeworm infestation. A variety of larvicidal agents are under investigation.

New concepts are emerging from recent clinical experience and laboratory investigation. The normal life cycle of cysticerci demonstrates surprising efficiency, with sites of predilection that confer enormous selective advantage—that is, muscle (thus maximizing transmission to other carnivores) and brain (enhancing a pig's vulnerability to predation). This apparent efficiency actually arises from complex host-parasite interactions, and recent observations shed important light on the pathogenesis of infection and clinical disease.

Many cysticercotic patients have no detectable immune response to cysticercal antigens.[18] This intriguing observation has led to the concept of selective immunosuppression of the host by the parasites, much as has been documented in cases of filariasis.[19] In experimental infections with various species of *Taenia,* parasite factors have been identified that can deplete complement, suppress lymphocyte activity, reduce eosinophil activity, kill granulocytes and other host cells and exhaust lymphocytes by polyclonal activation.[20] Related parasites can cleave host immunoglobulin attached to their surface into bound F_{ab} and free F_c components, covering antigenic sites but aborting further cell- or complement-mediated defenses.[21] Some intriguing cysticercal defense mechanisms are not immune-related;

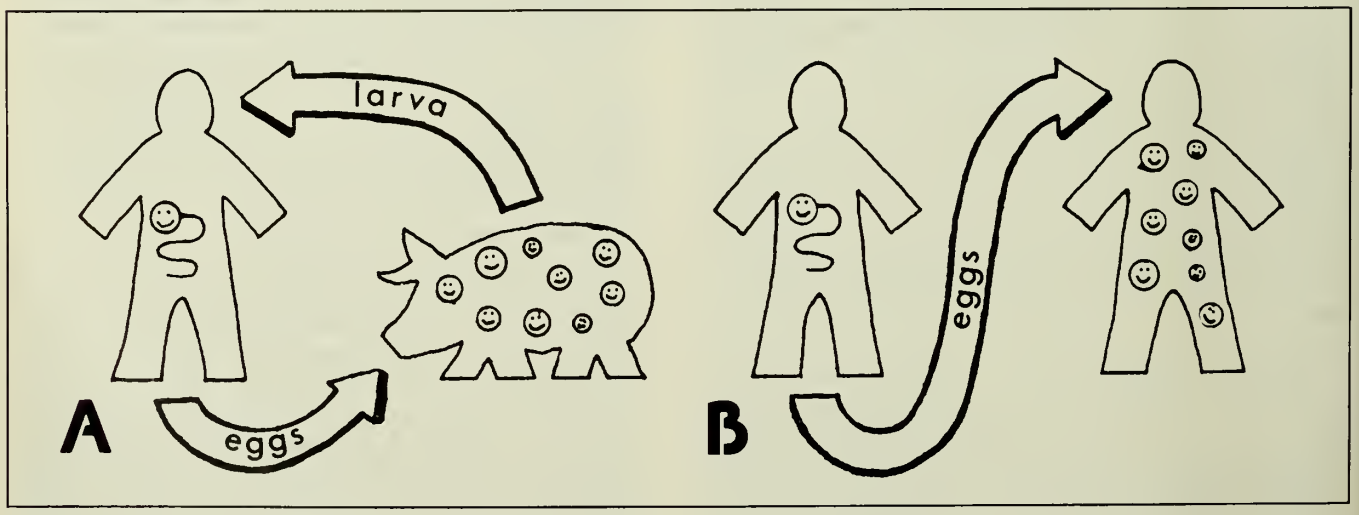

Figure 1.—Life cycle of *Taenia solium.* **A,** Taeniasis (infection with pork tapeworm) results when humans eat larvae in poorly cooked pork. Eggs passed in feces are then eaten by pigs, with release and migration of larvae (swine cysticercosis) completing the normal life cycle. **B,** Cysticercosis results when tapeworm eggs are ingested by another human, leading to diffuse infection with larvae. Autoinfection is possible by the fecal-oral route or (it is postulated) by reverse peristalsis of tapeworm segments into stomach, where eggs are released.

an example is the secretion of factors that inhibit host trypsin and chymotrypsin, thus preventing digestion while the embryo traverses the gut lumen.[22] Additionally, the fibrous capsule surrounding a cyst provides at least a partial physical barrier to host immune defenses.[20] These and other postulated mechanisms contribute to maintaining larval viability in the host (Figure 2). Apparently all these mechanisms are relatively specific for parasitic antigens or for the parasites' immediate vicinity in tissue (or both); there is no clinical or laboratory evidence for a generalized immunosuppression in patients who have cysticercosis.

When cysticerci die, their death prompts an intense inflammatory reaction. If current theories of immune interference are correct, this reaction stems not only from release of antigen by the dying worm, but also from a cessation of active immunosuppression. Onset or worsening of symptoms often coincides with this intense tissue response.[6] Confirmation of this natural history in living hosts is now available by sequential CT scanning.[23] Exacerbation of seizures, focal deficit or intracranial hypertension may be accompanied by CT findings of florid edema or contrast enhancement, which resolves over a course of weeks to months.

These observations lead to new perspectives on treatment. Insight into host immune defenses has stimulated considerable progress in developing vaccines, dependent primarily on an adequate supply of suitable antigen.[20] In a patient with already established infection, however, the question is whether killing the cyst is a good idea or a bad idea.[24]

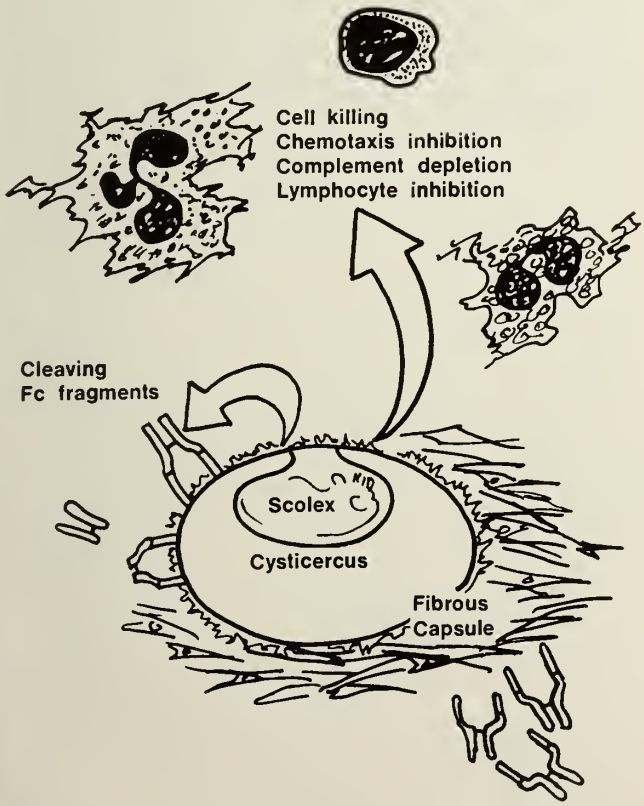

Figure 2.—Postulated mechanisms that promote survival of the cysticercus in an immunocompetent host. See text for details.

Several agents have been developed that are effective against cysticerci both in vitro and in vivo, most notably praziquantel.[25] Initial uncontrolled experience has been favorable,[26-28] but controlled trials are needed for several reasons. First, by killing the larvae, host immune defenses will be released from active suppression, which may result in a harmful acute inflammatory response. The specter of iatrogenically creating a lethal encephalitis cannot be dismissed[27,28] but perhaps will be preventable with concomitant steroid administration. Children should probably be treated more cautiously because of their predisposition to the encephalitic form[29] and to reactive brain swelling in general. Second, we now know that the larvae are often dead when a patient presents with symptoms. In this setting, the only value of praziquantel will be to eliminate any remaining viable worms. Last, the most debilitating symptoms result from chronic inflammation around nonviable cysts—a long-term process that may be unaffected or even accelerated by this therapy. In early trials praziquantel has already been noted to acutely worsen the meningitic response.[28]

As McCormick has suggested,[30] taeniacidal therapy may be more useful in certain clinical subgroups. Multiple parenchymal lesions may provide the best rationale for therapy. The patients with meningitis and hydrocephalus have the most refractory clinical course, but because their chronic inflammatory response is usually directed against already-lifeless cysts, they probably have the least to gain from larvicides. In a recent two-year follow-up on 100 patients receiving praziquantel, 16 deaths were recorded, of which 14 were apparently directly due to complications of continued subarachnoid inflammation.[31,32] Although the overall results included 40% cured and 43% at least slightly improved, our experience[1] and that of others[2-5] confirm the benign natural history of cysticercosis in most patients. Praziquantel therapy probably improves somewhat on this natural history, but the effect is hard to demonstrate.

Recently praziquantel has been released in the United States, approved for the treatment of other parasitic diseases. In our initial experience the drug is well tolerated. At least in adult patients, toxic effects of worm death have responded well to empirical steroid coverage. Unless patient and family compliance is virtually guaranteed, admission to hospital is appropriate at least for the first several days of therapy.

Another new and alarming perspective is epidemiologic: the documentation of transmission within the United States, as evidenced by the Los Angeles County series where seven patients had never left this country.[2] According to current knowledge, the establishment of new permanent foci in the US should not occur without infection of the pig population as well. This appears unlikely, at least in urban environments. Nevertheless, tapeworms are long-lived and usually produce no symptoms, and a single human carrier could serve as a

cysticercosis vector for many years.[33] Clearly, this issue merits careful public health consideration.

In summary, cysticercosis holds both threat and promise to our society. The threat is of a disease that causes major human and economic ravages in the Third World, now gaining a foothold in the United States, where it shows the potential to become endemic. The promise is that by studying this disease we can help lighten a major economic burden on the underdeveloped countries and learn more about the complex relationship between infection and immunosuppression—now of urgent interest for other reasons.[34] The newfound importance of this disease in the United States serves as continuing testimony to the interdependence of developed and developing countries.

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Outpatient Adult Inguinal Hernia Repair

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Repair of adult inguinal hernia has been done on an outpatient basis at our surgical facility for the past six years. In 616 consecutive repairs, complications have been remarkably few: one patient was electively admitted to hospital, two hernias have recurred and one patient needed to be catheterized. Patient acceptance has been enthusiastic.

(Lee RH, Marzoni FA, Cannon WB, et al: Outpatient adult inguinal hernia repair. West J Med 1984 Jun; 140:905-906)

Our early experience with outpatient inguinal hernia repair in adults was so zealously endorsed by the patients that we were encouraged to use this technique extensively. Now, as experience has grown, we feel that doing the repair on an outpatient basis is the method of choice for most patients.

Outpatient inguinal hernia repair is not new. As early as 1908 inguinal hernias were being repaired in children without admitting them to hospital, and this approach is well established worldwide. In 1955 Farquharson in Scotland,[1] dismayed by the long list of 447,000 patients awaiting operations in Great Britain, reported on 485 outpatient hernia repairs. His patients were sent home by ambulance and watched by the referring general practitioner and a visiting nurse team. Even though 11 had to be admitted to hospital, his overall results were very good. Stephens and Dudley organized a careful program for outpatient surgical procedures in Aberdeen (also Scotland) in 1961, primarily designed for inguinal hernia and varicose vein therapy. Their motivation was a waiting list of more than two years for hospital beds and they were successful in beginning to reduce the waiting time.[2] They had no higher incidence of complications and encouraged more widespread use of their methods. Others agreed[3-6] and the soundness of this method began to accumulate support. Resistance of surgeons, anesthesiologists and, in the United States, of insurance companies—if one can believe that—has consistently delayed the increased use of the outpatient mode for adult inguinal hernia repair.

In recent years in response to the tremendous pressures for medical-cost containment, there has been renewed interest in expanding the scope of outpatient surgery. Free-standing ambulatory surgeries ("surgicenters") have sprung up like mushrooms over the country. To meet the cost efficiency of these units, hospitals have developed dedicated ambulatory surgical units in which the entire outpatient operation is streamlined. These centers cater to the specific needs of patients, surgeons, anesthesiologists and staff where early discharge with a comfortable patient is the declared goal.

In 1976 a free-standing ambulatory surgical facility was constructed nearby, and our interest in outpatient procedures and particularly in inguinal hernia repair was stimulated. In this report we review 616 consecutive cases of adult patients with inguinal hernia operated on in this facility.

Initially patients were selected with great care, seeking younger patients with uncomplicated inguinal hernias. As our experience and confidence grew, however, older patients were added and we found they did as well or better than their younger counterparts. Patients with significant prostatic enlargement, insulin-dependent diabetes, cardiac disease and major respiratory insufficiency are generally still being operated on as inpatients. Others with controlled hypertension, asthma, coronary artery bypass, myasthenia and many other medical illnesses are cautiously being treated in the ambulatory center.

All types of hernias are repaired: direct, indirect, femoral, recurrent, sliding, bilateral and many ventral and umbilical hernias. Many ancillary procedures have been done, including vasectomy, hydrocelectomy, vein ligations, circumcisions, testicular biopsies, orchiopex-

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ies, removal of assorted nevi and lipomas and anal procedures.

Patients and Methods

In all, 616 consecutively treated adult patients with inguinal hernia operated on in our surgicenter are the subject of this study. The age range is 16 to 83 years. For the purpose of this study, pediatric patients are defined as those from 0 to 15 years and have been excluded. On admission to the facility, a history is taken and physical examination is done by the anesthesiologist. A patient's medical record from the Palo Alto Clinic is brought to the facility and available for the anesthesiologist and surgeon to review. Hemoglobin and urine are routinely analyzed in all patients. If a recent electrocardiogram is not in the medical record of patients older than 50 years, one is done before operation. If a patient is taking antihypertensive medication, recent serum sodium and potassium levels are reviewed. A chest x-ray study has usually been done sometime before the admission and, if not and indicated, one is done at the surgicenter. Preoperative medication usually is not given because it is hoped a patient will awaken promptly in the recovery room. The patient is prepared in the operating room and the operation is done under local, regional or general anesthesia depending on the preference of the patient, the assessment of the anesthesiologist and the desires of the surgeon. Of the patients in this series, 20% received local or regional anesthesia, the rest general. Bupivacaine hydrochloride, 0.5%, is the local anesthetic of choice, and during each procedure now done under general anesthesia bupivacaine is used to fully block the operated area just as if no general anesthetic were used. The long-acting action of bupivacaine is in our opinion one of the main reasons that the outpatient mode of operation for inguinal hernia has been so well received by patients and that complications have been so infrequent. With this anesthetic combination patients awaken with no pain. A Bassini repair is usually carried out for indirect inguinal hernias, an Andrews or Cooper's ligament (McVay) repair for direct hernias and a Cooper's ligament repair for femoral ones. Continuous size 00 prolene suture is usually used for the fascial repair, and the skin is closed with a subcuticular fine Vicryl, staples or prolene suture. The scrub nurse doubles as surgical assistant. On awakening in the recovery room, a patient is ambulated and urinates before discharge. Patients have almost no pain at the time of discharge with the bupivacaine effect still present. The total time in the facility averages three hours. A written set of instructions concerning activity, dressings, bowel movements and medication is given to the patient in addition to oral instructions by the surgeon. Acetaminophen with codeine or oxycodone hydrochloride is usually given to patients for pain relief. They are usually seen in the office in 48 to 72 hours when the dressing is removed, additional ambulation encouraged and they are told they can resume taking showers. Patients are encouraged to return to work about one week following the operation unless heavy work is involved.

Results

There are 616 patients in this series and the follow-up is from six years to six months. No patient has died. One patient who had no family to look after her was admitted to hospital, no other patients have needed hospital care. One patient needed to be catheterized. We have had two recurrences, in both cases where repair had been done originally with interrupted sutures on the fascial layer, a procedure now abandoned in favor of continuous suture. There have been four cases of superficial suture reactions, none of significant wound infections, one case of scrotal hematoma and one patient had severe postoperative constipation requiring office visits and enemas. Most patients have found it to be an extremely satisfying experience and would elect it again. Two patients emphatically stated that they would have a hospital repair if needed again.

Comment

The cost savings achieved by doing a procedure on an outpatient basis with its efficiencies compared with today's charges for inpatient services are clearly apparent. In the case of inguinal hernia repair, these include a savings of room charges, laboratory charges, recovery room charges, medication charges and surgical assistant fees. There is a substantial saving of time on the part of patients and surgeons. We believe that these all make a clear case for selecting the outpatient mode as the method of choice for most adult inguinal hernia repairs.

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Maintenance Requirements of L-Thyroxine in the Treatment of Hypothyroidism

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By analyzing data from 68 hypothyroid patients ranging in age from 15 to 75 years who had been maintained in a euthyroid state for at least a year with oral levothyroxine sodium therapy, we attempted to determine whether there was a correlation between L-thyroxine dose and body weight or patient age. The mean replacement dose of L-thyroxine was 186 μg a day ±69.6 or 2.76 μg per kg of body weight a day ±0.82. There was a significant correlation between L-thyroxine dose and body weight (P<.001), but due to the small number of patients studied who were older than 65 years of age, no correlation was noted between L-thyroxine dose and age.

(Kehoe WA Jr, Dong BJ, Greenspan FS: Maintenance requirements of L-thyroxine in the treatment of hypothyroidism. West J Med 1984 Jun; 140:907-909)

Patients who have newly diagnosed hypothyroidism are frequently started on a regimen of levothyroxine sodium at a dose that is based on their clinical state. Thus, young, otherwise healthy patients are often given full replacement doses whereas older patients—those with long-standing hypothyroidism and patients with underlying cardiovascular diseases that may be aggravated by thyroid hormone therapy—are started at lower doses that are then cautiously titrated upwards. Factors such as age and body weight have been reported to affect the dose requirements for attaining a euthyroid state.[1-9]

Replacement doses of 200 to 400 μg a day of L-thyroxine were routinely recommended through the early 1970s.[1] These higher doses were considered necessary to make up for the lack of triiodothyronine administration. Because, however, it is now widely recognized that a major portion of circulating triiodothyronine results from the peripheral monodeiodination of L-thyroxine, these earlier dosage recommendations offer no therapeutic advantage and often produce a toxic effect.[2] Thyroid-stimulating hormone (thyrotropin) radioimmunoassay, a more sensitive indicator of euthyroidism, confirms euthyroidism when doses of 100 to 200 μg a day of L-thyroxine are administered.

Age and body weight appear to be important determinants of thyroxine requirements, though the exact effect of these variables is unclear. Investigators have not evaluated the effects of weight but have reported doses in micrograms per kilogram a day, suggesting a correlation between dosage and weight.[3-5] Nilsson and co-workers in 1977 reported that L-thyroxine requirements did not correlate with body weight[6] while other investigators[1,7] found significant correlations. Similar dosage relationships have been noted with age.[1,7-9] Elderly patients appear to have reduced thyroxine requirements,[7] whereas increased requirements (3.5 to 3.8 μg per kg a day) have been found in the pediatric population.[8,9] Thus, the effects of weight and age on adult L-thyroxine requirements need further clarification. The following study was undertaken to evaluate such effects.

Patients and Methods

The files of one clinician (F.S.G.) were reviewed for patients meeting the following criteria:

- their hypothyroidism is due to Hashimoto's thyroiditis, radioiodine therapy, thyroidectomy, radiation exposure or an idiopathic cause;

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- they are receiving thyroid replacement rather than nodule suppression therapy;
- hypothyroidism has been documented based on their clinical state and serum thyroxine and thyrotropin values before initiation of therapy;
- euthyroidism has been maintained by a constant L-thyroxine dosage regimen for at least a year, and
- there has been no known administration of drugs or coexisting disease states known to alter thyroid function or laboratory values.[10]

A total of 68 patients met the criteria for inclusion in the analysis. For each patient, data recorded during retrospective review of the chart included diagnosis, age, weight, sex, L-thyroxine dose and serum thyroxine and thyrotropin values. Data were analyzed using the Statistics Package for Social Sciences (McGraw-Hill) at the University of California, San Francisco, Computer Center.

Results

The charts of 13 men and 55 women were reviewed. Table 1 shows the population data. The most common cause for the hypothyroidism was radioiodine therapy followed by thyroidectomy, Hashimoto's thyroiditis, idiopathic hypothyroidism and radiation exposure.

Table 2 shows the clinical data obtained from the chart review. All patients were clinically euthyroid. The mean dose of L-thyroxine for this patient population was 186 μg a day ±69.6 (standard deviation [SD]). When calculated on a weight basis, the value was 2.76 μg per kg a day ±0.82 (SD), or 1.25 μg per lb a day.

Figures 1 and 2 show the results of the regression analysis. When dose was evaluated as a function of body weight, the correlation coefficient was .56 ($P<.001$). The correlation coefficient for dose as a function of age was −.11 ($P>.05$). Body weight did not significantly decrease with age in this population ($r=-.102$, $P>.05$).

TABLE 1.—*Patients Being Treated With Levothyroxine Sodium for Hypothyroidism*

No. of Patients (sex)	68 (13 ♂, 55 ♀)
Age, years* (range)	37±15 (range, 15 to 75)
Weight, kg*	66.9±14.3 (range, 46 to 100)
Cause of hypothyroidism *(Number of Patients)*	
Radioiodine therapy	21
Thyroidectomy	20
Hashimoto's thyroiditis	19
Idiopathic	5
Irradiation	3

*Mean ± standard deviation.

Discussion

Most investigators have found that the majority of hypothyroid patients can be maintained on a regimen of L-thyroxine at doses of 100 to 200 μg a day. Our findings support this.

The results of the present study are in agreement with those of Stock and associates (1974) and Rosenbaum and Barzel (1982) concerning the effect of body weight on dose.[1,7] L-Thyroxine requirements increased significantly with total body weight. Our value of 2.76 μg per kg a day is slightly higher than that found by

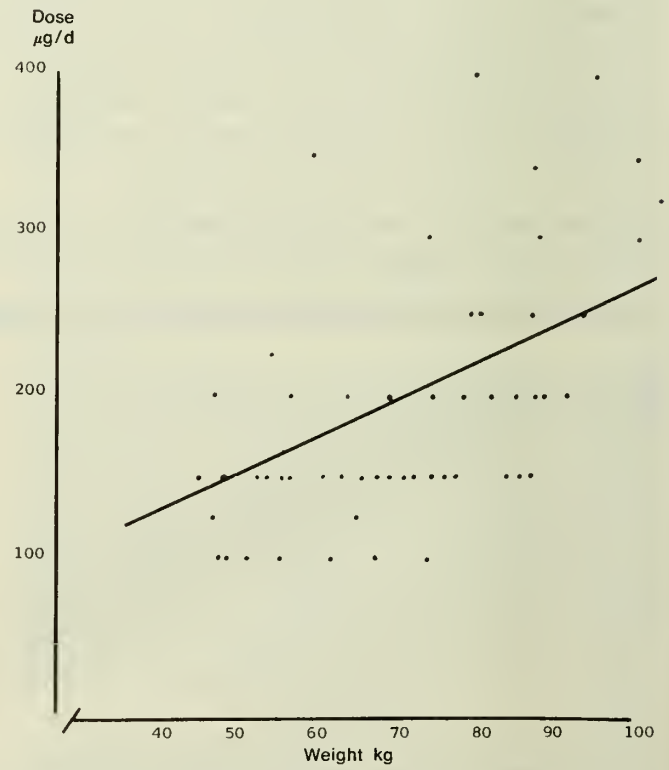

Figure 1.—Correlation between L-thyroxine dose and weight: There was a significant correlation between L-thyroxine dose and body weight, $r=.56$ ($P<.001$).

TABLE 2.—*Clinical Data for 68 Patients With Hypothyroidism Being Maintained on Levothyroxine Therapy*

Number of Patients	*Final Serum Thyroxine Level μg/dl* Mean±SD	Normal	*Final Serum TSH Level μU/ml* Mean±SD	Normal	*Mean Dose μg/d* Mean±SD (μg/kg/d)
68	11.3±2.3	5-12			
29			<2.00	<10	
39			4.54±1.85		
68					186±69.6 (2.76±0.82)

TSH=thyroid-stimulating hormone (thyrotropin), SD=standard deviation

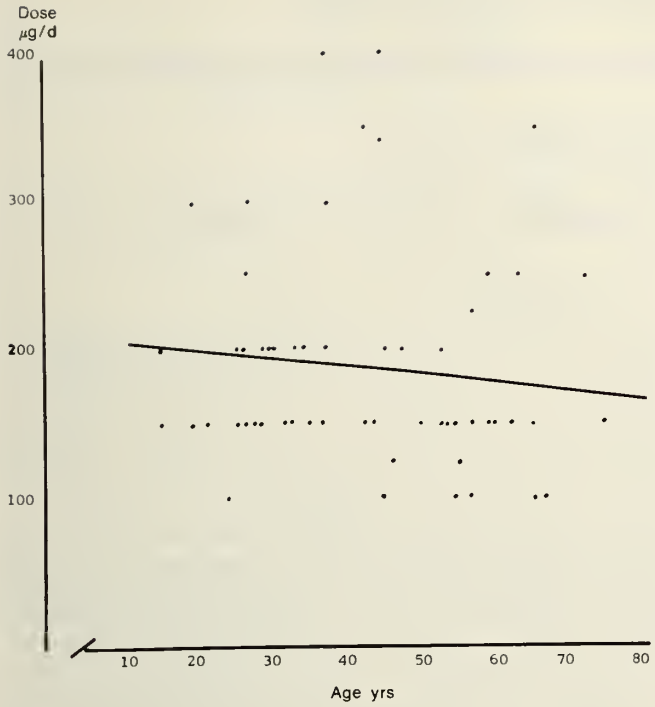

Figure 2.—Correlation of dose and age: There was no significant correlation between dose and age, $r = -.11$ ($P > .05$).

other investigators (1.86 to 2.25 μg per kg a day). Two possible explanations may account for this higher value:

First, dosage adjustments of 50-μg increments were commonly made in these patients. Even though they were euthyroid, the effect of smaller dosage increments such as 25 μg could not be determined from this study. It is possible that euthyroidism could still be maintained if smaller adjustment increments were used, though our criteria may not be sensitive enough to discriminate between doses differing by only 25 μg or less.

Second, seven of our patients were noted to require doses of more than 4 μg per kg a day. All were euthyroid as defined above and no reason for the increased requirements could be determined. Possibilities include noncompliance and erratic thyroxine absorption, which may range from 50% to 90%.[11]

The turnover rate of L-thyroxine decreases with age due to decreases in both the distribution space after 60 years and the fractional turnover up to age 70 years of age, so that the net result is a 50% reduction in thyroxine degradation between the ages of 20 and 80 years.[12,13] No effect of age on L-thyroxine requirements was demonstrated in this population. The patients studied by Rosenbaum and Barzel[7] showed a significant decrease in dosage requirements continuously with age. However, their population also showed a decrease in body weight with age, the effects of which were not ruled out in the regression of dose with age. When their patients were separated into groups of younger and older than 65 years of age, a significant difference in dosage requirements was seen (2.09 and 1.86 μg per kg a day, respectively).

There are several possible explanations for the differences between the results of their study and those of the present one. First, the present population did not show a continuous decrease in weight with age, which may have affected the results of Rosenbaum and Barzel.[7] Second, the present population included only five patients older than 65 years, so that a comparison of an older with a younger group is not possible. It may be that the effect of age only becomes clinically significant after age 65. Last, the dose differences cited above would represent a 16-μg-a-day dose difference in a person weighing 70 kg. The sensitivity of current diagnostic tests to pick up this difference could not be evaluated in this study.

In conclusion, L-thyroxine requirements in the present population were significantly correlated with total body weight. No effects of age were noted, however, due to the small sample studied. Further investigations are required to determine which adult age groups show clinically significant differences in L-thyroxine requirements.

Addendum

The dosage recommendations in this report are based on tablets of L-thyroxine (Synthroid) manufactured before 1983 by Flint Laboratories division of Travenol Laboratories, Inc. In 1983 the tablet was reformulated to allow assay with high pressure liquid chromatography. This resulted in 100% bioavailability compared with the previous tablet, which had only 78% of expected potency.[14,15] Thus, when using the new tablets, a dosage reduction of 20% to 30% may be necessary to maintain euthyroidism and to prevent clinical toxicity.

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Medical Progress

Clinical Detection of Acute Vestibulocerebellar Disorders

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The acute onset of vertigo, nystagmus and postural instability, without brain-stem signs, is commonly attributed to a disorder of the labyrinth, the vestibular, sensory end organ. Identical symptoms can occur, however, with discrete infarctions or hemorrhages involving the central vestibulocerebellum. Whereas acute labyrinthine disorders are usually benign and self-limited, vascular injuries of the cerebellum may produce swelling, compression of the brain stem and acute hydrocephalus one to four days after the onset of symptoms. Therefore it is important to accurately distinguish between labyrinthine and vestibulocerebellar disorders with the neurologic examination. Acute labyrinthine disease causes unidirectional nystagmus with past-pointing and falling in the opposite direction of the nystagmus, environmental vertigo in the same direction and suppression of the nystagmus with visual fixation. Disorders of the vestibulocerebellum do not produce this consistent pattern of findings.

(Hotson JR: Clinical detection of acute vestibulocerebellar disorders [Medical Progress]. West J Med 1984 Jun; 140:910-913)

Among the diverse complaints of dizziness lies a singular clinical syndrome characterized by the acute onset of persistent vertigo, nausea and vomiting and postural instability. In patients with this problem, little is found on examination beyond nystagmus and a tendency to fall or list in one direction when standing and walking. This clinical condition is best referred to as an acute vestibular syndrome or vestibulopathy, for it has many causes besides the commonly attributed acute labyrinthitis.

Many clinicians consider this disorder to be due to a disease process of the vestibular end organs and in particular the semicircular canals. In most cases this understanding may be correct; however, it is not widely appreciated that an acute disorder of the inferior portions of the cerebellum, called the vestibulocerebellum, may also produce an acute vestibular syndrome with a paucity of signs pointing to either the cerebellum or brain stem.[1] There are two causes of this central vestibular disorder, namely a distal occlusion of the posterior inferior cerebellar artery infarcting the vestibulocerebellum or a discrete hemorrhage in or adjacent to the same location. Patients with these disorders are seen at least three to four times a year in a general hospital setting and these disorders are a diagnostic consideration even more frequently.

It is particularly important to recognize an infarction or hemorrhage affecting the vestibulocerebellum because associated swelling may lead to compression of the brain stem and rapidly produce coma and a respiratory arrest. At the same time, however, to treat every vertiginous patient as if they have a potentially fatal stroke is inappropriate. Therefore, a practical, clinical means of separating acute, but benign, labyrinthine disorders from vestibulocerebellar strokes is a requirement of many physicians and the focus of this review.

Functional Anatomy

A simplified approach to the vestibular system is to divide it into three parts (Figure 1).[2] The peripheral labyrinth (the semicircular canals and otoliths) is a sensory end organ for detecting head acceleration and displacements. The vestibular nuclei lie in the brain stem and initiate contralateral vestibulo-ocular responses and ipsilateral vestibulospinal reflexes to maintain stable vision during head movements and stable

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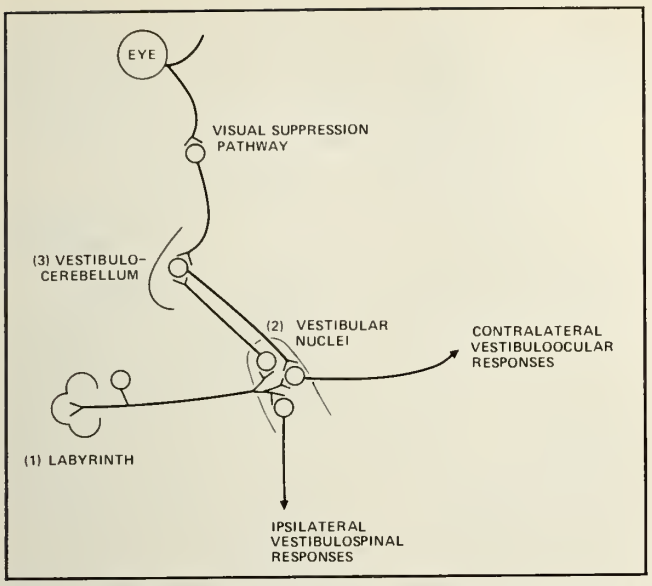

Figure 1.—Schematic drawing of a unilateral vestibular system showing the relationships of (1) the labyrinth, (2) the vestibular nuclei and (3) the vestibulocerebellum. Sensory inputs from the labyrinth cause contralateral rotation of the eyes via vestibulo-ocular pathways or ipsilateral increased extensor tone in the extremities via the vestibulospinal pathways. The vestibulocerebellum mediates the visual suppression of vestibulo-ocular responses.

posture during body movements.[3,4] The third component of the vestibular system is the vestibulocerebellum, which modulates the output of the vestibular nuclei and includes the flocculus, nodulus, uvula and fastigial nuclei and portions of the vermis.[2] For clinicians it is important to know that the vestibulocerebellum mediates the visual suppression of vestibulo-ocular responses, because testing this suppression provides a means of measuring vestibulocerebellar function (see below).[5,6]

When an acute disorder involves the central vestibular nuclei, there are so many important adjacent brainstem structures that additional signs of a brain-stem disorder are usually apparent. Thus, separating an acute peripheral from a vestibular nucleic disorder is usually not difficult. This clinical distinction, however, is less true for acute disorders involving the vestibulocerebellum. My main point is that a patient with infarction or hemorrhage limited or adjacent to the vestibulocerebellum may present with clinical symptoms and findings quite similar to an acute labyrinthine disorder.[1]

Acute Vestibulocerebellar Disorders

The documentation that a stroke of the vestibulocerebellum may present solely with an acute vestibular syndrome comes from a clinicopathologic study of three patients with discrete infarctions of the vestibulocerebellum.[1] The only clinical signs were vertigo, nausea and vomiting, postural and gait instability and horizontal nystagmus. Cerebellar dysmetria and brainstem signs were *not* present. In two of the three patients cerebellar swelling with brain-stem compression developed within two days of the onset of symptoms. This report documented the existence of a potentially fatal, acute vestibular syndrome due to an infarction involving the vestibulocerebellum. Since this initial report similar cases have been found by computed tomography (CT) of the brain.[7] Observations using CT scanning have also found that small, discrete hemorrhages in or adjacent to the vestibulocerebellum may produce predominantly vestibular symptoms.[8,9] This point and the need for increased awareness by physicians of various specialties is illustrated by the following case report.

Report of a Case

While at work a 62-year-old man had the rapid onset of vertigo, nausea, a mild occipital headache and imbalance while standing or walking, with a tendency to fall to the left. He could walk but required assistance. Besides smoking and his age, there were no risk factors for stroke. The patient was initially seen in an emergency room and two days later by an otolaryngologist.

Examination showed no abnormalities except for left, horizontal, gaze-induced nystagmus, a tendency to fall to the left during Romberg testing and a mild high-frequency hearing loss bilaterally. The finger-to-nose test was noted to be done well and it was specifically stated that no cerebellar signs were present. Visual suppression of the nystagmus was not examined. The clinical diagnosis was acute labyrinthitis and the patient was sent home.

Over the next two weeks the severe, continuous vertigo and imbalance were replaced by a position-induced vertigo and unsteadiness. Because of these continued complaints the patient was referred for a neurologic evaluation. On examination there was no evidence of nystagmus, postural instability, limb dysmetria or position-induced symptoms and signs. The initial observation that the direction of nystagmus and falling were the same deviated from findings indicating an acute labyrinthine disorder (see below for detailed discussion). Also, the headache and sudden onset of symptoms in an elderly patient suggested a cerebrovascular disorder. Therefore, a CT scan of the brain was done and showed a resolving, paravermian, 1- to 2-cm cerebellar hemorrhage (Figure 2).

Two months after the onset of his acute vestibular syndrome, the patient's positional vertigo had lessened but still occurred and a repeat CT scan showed radiographic resolution of the hemorrhage without evidence of an underlying vascular malformation.

Comment. Lack of awareness of the neurologic findings indicative of a labyrinthine disorder led to the initial diagnostic error. This patient was fortunate in that he had a benign cerebellar hemorrhage. There are similar cases in which the initial diagnosis was an acute labyrinthitis and the cerebellar hemorrhage went on to compress the brain stem within the next two days.

Clinical Evaluation

The distinction between an acute vestibulocerebellar stroke and a labyrinthine disorder depends in part on

the clinical setting but eventually is dependent on the findings of a neurologic examination. The neurologic examination is used to determine whether or not a case of acute vestibular syndrome has all the features of a disorder of the labyrinth. If the findings are not consistent with those of a labyrinthine disorder, then an acute process of the vestibulocerebellum must be sought.

In acute labyrinthine disorders the findings are the same as in normal persons after unilateral ice-water caloric testing.[10] Both a destructive disorder of the labyrinth and ice-water perfusion of the vestibular end organ result in a decrease in the efferent input from the ipsilateral vestibular nerve. This causes unidirectional, horizontal nystagmus, often with a rotatory component, and falling or listing during Romberg testing that is in the *opposite* direction of the fast component of the nystagmus. Caution must be used, however, in the direction of falling during Romberg testing. Some persons overcompensate for a feeling of unidirectional falling and may actually fall or list in a direction opposite to which they feel and mislead the examiner. Thus, it is important to instruct a patient not to try to correct or compensate for a feeling of falling.

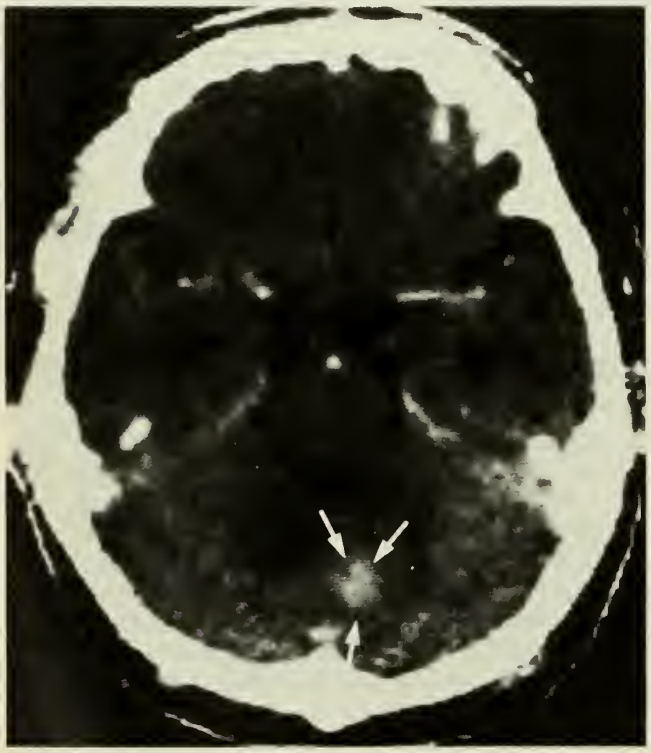

Figure 2.—Computed tomographic scan of the brain showing a small cerebellar hemorrhage **(arrows)** abutting the left vermis and the deep nuclei in the roof of the fourth ventricle.

TABLE 1.—*Clinical Features of Acute Labyrinthine Versus Acute Vestibulocerebellar Disorders*

	Acute Labyrinthine Disorder	*Acute Vestibulo-cerebellar Disorder*
Nystagmus fast phase	→	→
Direction of Romberg fall and past-pointing	←	→
Environmental vertigo	→	↔
Visual suppression	Yes	No
Brain-stem signs	No	Not initially
Tinnitus/deafness	Occasionally	No

Persons with acute labyrinthine disorders frequently have a sensation of environmental rotation or vertigo and the direction of rotation is in the *same* direction as the fast component of nystagmus. The direction of environmental rotation is determined by a patient's subjective sensation during eye closure. Even further evidence of a peripheral vestibular disorder is demonstration of the visual suppression or inhibition of the unidirectional nystagmus. The velocity of the slow phase of labyrinthine-induced nystagmus decreases 50% with visual fixation on a target and increases with removal of fixation.[5,6] This visual suppression of nystagmus requires an intact vestibulocerebellum and thus may help differentiate a labyrinthine from a cerebellar disorder. It is best tested by observing the eyes behind Frenzel lenses. However, it can also be tested by observing the slow phase of nystagmus with an ophthalmoscope focused on the optic nerve head of one eye while the patient looks at a fixation point with the opposite eye.[11] Alternating between covering and uncovering the single fixating eye permits a qualitative bedside examination of the visual suppression of vestibular nystagmus.

In summary, a person with an acute labyrinthine disorder may have unidirectional nystagmus with past-pointing and falling in the *opposite* direction and environmental vertigo in the *same* direction of the fast phase of nystagmus. The velocity of the nystagmus slow phase may be reproducibly suppressed by visual fixation. In contrast, acute vestibulocerebellar disorders do not conform to the above findings (Table 1). The nystagmus may be bidirectional, unidirectional or even absent. When unidirectional, the direction of falling is usually the same as the fast component of the nystagmus, similar to the case reported above. The direction of vertigo varies.[1] Visual fixation may not suppress the nystagmus and in some patients it even enhances its intensity. Therefore, in the elderly and in all persons at risk for stroke, any deviation from the expected findings of a unilateral labyrinthine disorder requires prompt evaluation of a cerebellar infarction or hemorrhage.

In this situation, the next mandatory diagnostic step is a CT scan of the brain with particular attention to the posterior fossa and fourth ventricle. Whereas a CT scan will rapidly determine whether or not a cerebellar hemorrhage is present, a cerebellar infarction is often not apparent on the initial study.[12] Therefore, even with an initially normal CT scan, a cerebellar infarction may be present that can swell and compress the brain stem in the next two to three days. For these reasons, patients at risk for stroke should be observed in a hospital setting. If over the ensuing 48 to 72 hours the

symptoms definitely abate, which can happen in both a labyrinthine and a vestibulocerebellar disorder, a safe clinical course is likely. If a patient's condition does not improve, close observation and a repeat CT scan one to two days after the onset of symptoms is done to look for evidence of cerebellar swelling and encroachment on the fourth ventricle.

Treatment

In general, the treatment of a cerebellar hemorrhage is prompt surgical evacuation and that of a cerebellar infarction is close observation. Exceptions to each approach exist, however. Small cerebellar hemorrhages may have a benign course similar to the case described above.[9,13] These cerebellar hemorrhages may not require surgical intervention if the patient is alert, brainstem signs are absent and the hemorrhage is smaller than 3 cm.[8,9,14] There should be no evidence of hydrocephalus or compression of the brain stem on a CT scan done more than six hours after the ictus. (Hemorrhages rarely bleed more than six hours in a person with normal clotting factors and do not rebleed unless associated with a vascular malformation.)[15] This is also one stroke in which a strong argument may be made for the short-term use of steroids even though the efficacy can be questioned.

Whereas most cerebellar infarctions resolve simply with time, in some the cerebellum swells to such a magnitude that there is brain-stem compression and acute hydrocephalus requiring prompt posterior fossa surgical decompression[13] or ventricular drainage.[16,17] Progressive cerebellar mass lesions are notorious for extremely rapid deterioration with respiratory arrest. By being aware of this possible course and properly evaluating a case of acute vestibular syndrome, we may be able to prevent a stroke of the vestibulocerebellum from leading to such a dire situation.

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Specialty Conference

Fever and Pulmonary Infiltrates in a Patient With a Renal Transplant

Discussants

JAN V. HIRSCHMANN, MD; JAMES J. PLORDE, MD, *and* REX F. OCHI, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Assistant Professor of Medicine, and Philip J. Fialkow, Professor and Chairman of the Department of Medicine.

REX F. OCHI, MD:* A 42-year-old man was admitted to hospital in April 1983 because of cough, wheezing, abdominal pain and rectal bleeding. In November 1981 he had undergone successful cadaveric renal transplantation for chronic renal failure due to glomerulonephritis. Following transplantation, the serum creatinine level was about 2.9 mg per dl on immunosuppressive therapy consisting of prednisone, 25 mg a day, and azathioprine, 125 mg a day. Wheezing first developed in early March 1983 and the serum creatinine level was found to be 8.3 mg per dl. The patient was treated for transplant rejection with temporary hemodialysis, prednisone, 200 mg a day, and azathioprine, 150 mg a day. After the serum creatinine level fell to 4.0 mg per dl, the dosage of immunosuppressive agents was rapidly tapered over three weeks to prednisone, 80 mg a day, and azathioprine, 100 mg a day. In late March, multiple cutaneous abscesses developed around the right eye, left flank, umbilicus and groin, for which he was given cephalexin monohydrate, 500 mg by mouth four times a day. His prednisone dosage was tapered to 60 mg per day.

In early April the patient had increasing wheezing, dyspnea and purulent sputum. He also noted hematochezia and abdominal pain exacerbated by medication and relieved by meals or antacids. There was no history of allergies, fever, melena or the use of alcoholic beverages or aspirin.

The patient spent the first 12 years of life in Samoa and then lived in San Francisco until 1982. At that time he moved to Seattle where he worked as a furniture upholsterer. The patient's mother died of glomerulonephritis; his brother, still living in Samoa, has "kidney disease." Medication at the time of admission included prednisone, azathioprine, furosemide and a long-acting theophylline preparation.

On physical examination the temperature was 37.2°C, pulse 96 beats per minute, respirations 22, blood pressure 132/90 mm of mercury and weight 93.2 kg (down 2 kg from usual). The patient appeared cushingoid but otherwise well except for mild respiratory distress. There were diffuse expiratory and inspiratory wheezes, the abdomen was minimally tender in the subxyphoid region and there were several 0.5-cm furuncles on the back and perianal area. On rectal examination there were small amounts of bright red blood. There was no peripheral edema, and the remainder of the physical examination showed no abnormalities.

Arterial blood gas determinations done while the patient was receiving two liters of oxygen by nasal prongs gave the following values: pH 7.41, carbon dioxide partial pressure (P_{CO_2}) 32 mm of mercury, oxygen partial pressure (P_{O_2}) 135 mm of mercury and bicarbonate 20 mEq per liter. The hematocrit was 18% with moderate polychromasia and normal erythrocyte indices. The leukocyte count was 11,200 per μl with 5,820 neutrophils, 2,640 bands, 1,100 lymphocytes, 550 metamyelocytes, 220 myelocytes, 2 nucleated erythrocytes and no eosinophils or basophils. Serum electrolytes in mEq per liter were as follows: sodium 131, potassium 3.6, chloride 100 and carbon dioxide 22.

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Figure 1.—Chest roentgenogram showing diffuse interstitial infiltrates.

Other serum chemistry values included creatinine 5.1, calcium 9.1, phosphorus 4.3 and urea nitrogen 90 mg per dl. The albumin was 3.1 grams per dl, alkaline phosphatase 60 IU per liter and theophylline concentration less than 2.5 μg per ml. Sputum Gram's stain showed moderate neutrophils with mixed flora and many Gram-negative coccobacillary forms. Chest x-ray film showed no abnormalities. Nasogastric aspirate was guaiac-negative. Initial treatment included intravenous administration of aminophylline (theophylline 85% with ethylenediamine 15%), methylprednisolone, cephalothin sodium, cimetidine and two units of packed erythrocytes.

On hospital day 2 anoscopy and sigmoidoscopy showed a left lateral dilated hemorrhoid with superficial bright red blood from erosions. Methylprednisolone therapy was discontinued and prednisone therapy begun. On hospital day 3 the patient's epigastric pain was diminished and a barium enema study showed no abnormalities except for diverticulosis. On hospital day 5 the patient had worsening of chest and abdominal pain, and an upper gastrointestinal series showed a 6-mm duodenal ulcer. Antacids were added to the medical regimen. Arterial blood gas determinations done while the patient was breathing room air showed a Po_2 of 51 mm of mercury, the serum creatinine level was 6.3 mg per dl and a chest x-ray film showed changes typical of volume overload. He underwent hemodialysis with a dramatic reduction in symptoms. A sputum culture from admission grew *Hemophilus influenzae,* and the antibiotic therapy was changed to ampicillin.

On hospital day 6 the patient felt better but still had bilateral wheezing on chest examination and a mildly tender abdomen. The leukocyte count was 10,900 per μl with 7,740 neutrophils, 1,960 bands, 550 lymphocytes, 330 monocytes, 110 eosinophils, 110 metamyelocytes and 110 myelocytes. The serum amylase level was 190 IU per liter. On hospital day 7 the patient's creatinine level was 7.2 mg per dl and hemodialysis was repeated.

TABLE 1.—*Active Medical Problems in a Patient Who Has Had a Renal Transplant*

Multiple cutaneous abscesses	Duodenal ulcer
Wheezing, dyspnea, hypoxia	Diverticulosis
Gastrointestinal hemorrhage	Increased serum amylase
Abdominal pain	Fever
Anemia	Purulent, bloody sputum
Leukoerythroblastosis	Diffuse pulmonary infiltrates
Hypoalbuminemia	Gram-negative rods in blood and sputum

On hospital day 8 the patient's abdominal pain increased and his cough became productive of purulent blood-tinged sputum. His temperature was 39°C and weight 87.7 kg; a chest x-ray film showed diffuse interstitial infiltrates (Figure 1). A sputum Gram's stain showed 3+ neutrophils and 4+ Gram-negative rods. The antibiotic regimen was changed to cephalothin, tobramycin and trimethoprim-sulfamethoxazole (Cotrimoxazole).

On hospital day 9 the patient remained febrile and a Gram-negative rod grew from cultures of sputum and blood specimens. Further diagnostic studies were done.

Discussion

JAN V. HIRSCHMANN, MD:* Confronted with such a complex and puzzling case, I feel like the person who asked Fats Waller what jazz is. "Man, if you don't *know* what it is, don't mess with it," Waller answered. Wise counsel, but as Oscar Wilde said, there is only one thing to do with good advice—pass it along. Having done that, I'll now discuss the patient's illness.

In analyzing a complicated case, the best starting point is to list the identifying data and the current medical problems. The patient is a 42-year-old man who lived in Samoa until age 12. His residence in a tropical country 30 years ago may become crucial in the differential diagnosis. The other important history is the cadaveric renal transplant for chronic glomerulonephritis 1½ years ago, for which he received varying doses of immunosuppressive drugs, prednisone and azathioprine. The patient's present illness involves at least 14 problems (Table 1). In tabulating these, one should keep the possibly related conditions separate unless there is cogent evidence that they constitute a single diagnosis. For example, it is tempting to attribute the gastrointestinal hemorrhage to the duodenal ulcer, but the absence of blood in the nasogastric aspirate and the lack of melena make an upper intestinal tract source uncertain. Similarly, the fever, purulent sputum, diffuse pulmonary infiltrates and growth of Gram-negative rods in the blood and sputum specimens seem to indicate a pneumonia caused by enteric Gram-negative rods. The radiographic appearance of a mixed alveolar-interstitial pattern affecting the entire lung, including the apices, however, is very unusual for an uncomplicated Gram-negative

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TABLE 2.—*Systemic Infections Causing Skin Lesions in Immunodeficient Hosts*

Organisms	
Higher Forms of Bacteria	Viruses
Nocardia	Herpes simplex
Mycobacteria	Varicella-zoster
Fungi	Parasites
Candida	*Strongyloides stercoralis*
Cryptococcus neoformans	
Aspergillus sps	
Histoplasma capsulatum	
Coccidioides immitis	

bacillary pneumonia, and these features should initially be considered as separate entities.

The next step is to choose two or three prominent or distinctive features in the case, generate a differential diagnosis for each and determine whether the disorders listed can explain the patient's illness. I have chosen for discussion the cutaneous abscesses and pustules, the leukoerythroblastosis and the diffuse pulmonary infiltrates.

Before proceeding, however, one must acknowledge a methodologic and conceptual concern, well illustrated by two similes that Bertrand Russell proposed when asked to contrast his philosophy with Alfred North Whitehead's.[1(p62)] Russell said that he considered the world to be like a heap of shot, but that Whitehead saw it as a bowl of treacle. Russell viewed reality as multiple discrete entities; Whitehead, the great proponent of organic unity, saw homogeneity even among apparently disparate matter. The question in this patient is whether his current illness is a heap of shot or a bowl of treacle—several diseases or diverse manifestations of a single disorder. Ordinarily in differential diagnosis, especially in clinicopathologic correlations, the clinician heeds the guidance of a 14th century English monk, William of Ockham (1300 to 1349), who enunciated the principle called Ockham's razor: "Entities are not to be multiplied beyond necessity." If one disease explains everything, why invoke more? This dictum is usually appropriate with children and young adults, but as patients age or become immunocompromised, the concurrence of several diseases is frequent and the use of Ockham's razor can be misleading.

The patient's problem of multiple pustules is a good example. These may be nothing more than staphylococcal pyoderma or the nonspecific acneiform lesions common to patients receiving high-dose corticosteroids. The cutaneous manifestations of systemic infections in immunodeficient hosts, however, may appear trivial, emphasizing the importance of promptly obtaining specimens for culture, Gram's stains and biopsy specimens from persistent or peculiar skin abnormalities.[2] Disseminated infections caused by a variety of organisms, including bacteria, fungi, viruses and parasites, may produce skin lesions in renal transplant recipients or other patients with severely impaired cell-mediated immunity (Table 2).

Nocardia asteroides is an aerobic bacterium that may cause pneumonia when inhaled. From the initial pulmonary site *Nocardia* tends to disseminate hematogenously to two distant locations: the central nervous system—where it causes brain abscesses or meningitis—and the skin and subcutaneous tissue—where abscesses form that frequently create draining sinuses.[3] Microscopic examination of a specimen of pus may reveal the organism, a beaded, branching Gram-positive rod. It is acid-fast when stained with a weak acid solution and grows on many media, but colonies may become visible only after several days to weeks. The clinician should inform the laboratory of the possibility of nocardiosis to prevent premature disposal of the cultures. This progressive infectious disease is treatable with sulfonamides but can usually be eradicated in an immunocompromised host only with protracted therapy for at least 6 to 12 months. Co-trimoxazole (sulfamethoxazole-trimethoprim) may be the most effective antimicrobial agent.[4] Although nocardiosis could explain the pustules and cutaneous abscesses seen in the patient, this infection rarely involves the gastrointestinal tract, and the abnormality seen on chest x-ray film is typically a segmental infiltrate or multiple nodules rather than a diffuse, mixed alveolar-interstitial pattern.[5] Furthermore, there is no unique association with Gram-negative bacteremia.

Tuberculous or nontuberculous ("atypical") mycobacteria can cause skin lesions, most often nodules that ulcerate, but also abscesses or pustules.[6] Disseminated infections with nontuberculous mycobacteria, particularly *Mycobacterium chelonei* and *Mycobacterium haemophilum,* cause cutaneous lesions in renal transplant recipients.[7] These infections, however, rarely involve the gastrointestinal tract or the lungs, and there is no association with Gram-negative bacteremia. *Mycobacterium tuberculosis* can affect the alimentary canal, typically in the terminal ileum, where perforations may lead to Gram-negative bacteremia. The chest roentgenographic pattern of mixed alveolar-interstitial infiltrates is sometimes seen, but this appearance typically represents bronchogenic spread of a preceding cavitary lesion. This patient's admission chest film, however, showed no abnormalities. While hematogenous spread of tuberculosis to the lungs from a gastrointestinal site could occur, the radiographic pattern should be miliary, with multiple tiny nodules, not a mixed interstitial-alveolar infiltrate. Furthermore, cutaneous involvement with *M tuberculosis* is uncommon, even in an immunocompromised patient. For this case to be tuberculosis would involve more coincidences than in a Dickens novel.

The cutaneous lesions of systemic candidiasis are usually single or multiple erythematous papules or nodules rather than pustules, because the blood-borne organisms lodge in the dermis rather than the epidermis. Blood cultures are usually positive, typically for *Candida tropicalis,* and patients characteristically have cancer and neutropenia.[8] *Candida* may involve the gastrointestinal tract, usually as esophagitis (not clin-

ically evident in this case), but also as ulcerations in the stomach, small intestine and colon.[9] Because *Candida* rarely causes significant pulmonary disease[10] and commonly accompanies other infections, its typical roentgenographic appearance is uncertain, but the organisms should be found in a sputum Gram's stain and culture.[11] Systemic candidiasis usually develops in patients receiving extensive antimicrobial chemotherapy, especially while they are neutropenic. In this patient, therefore, disseminated candidiasis seems unlikely.

Cryptococcus neoformans most commonly causes nodular skin lesions, which may ulcerate, or areas of cutaneous erythema, warmth and tenderness resembling bacterial cellulitis. Abscesses, plaques, pustules or acneiform lesions occasionally occur.[12] India ink preparation of a skin aspirate may establish the diagnosis by showing budding yeasts surrounded by a thick polysaccharide capsule. Cryptococcosis is unlikely in this case because this organism rarely involves the gastrointestinal tract and has no particular association with Gram-negative bacteremia. Although pulmonary cryptococcosis may show many different radiographic appearances—focal pneumonia, nodules, masses, miliary pattern—a diffuse mixed alveolar-interstitial form is not among them.[13]

Aspergillus species, usually *Aspergillus flavus,* can cause cutaneous lesions, typically necrotizing skin ulcers with a black eschar,[14] which are usually primary infections. Hematogenous aspergillosis from a pulmonary focus can cause cutaneous abscesses, and the organism commonly affects the gastrointestinal tract, causing ulcerations and hemorrhage.[15] Most patients, though, are neutropenic and have received broad-spectrum antibacterial therapy. Furthermore, Gram-negative bacteremia due to intestinal perforation from an aspergillar ulcer would be unusual. Finally, the typical chest radiographic abnormalities are nodules or segmental infiltrates, often mimicking a pulmonary embolus because of the organism's tendency to invade vessels and cause thrombosis.

There is no epidemiologic information to incriminate histoplasmosis or coccidioidomycosis as this patient has not lived in endemic areas for either. The description of the skin pustules and abscesses makes herpesvirus infections unlikely. Although herpes simplex virus can cause pneumonia in an immunocompromised host, most patients have vesicular mucocutaneous lesions, and most with concomitant bacterial pneumonias have neutropenia.[16] The skin lesions in this patient were not vesicular and did not occur in a dermatomal pattern, excluding herpes zoster as well. A parasite that can cause cutaneous lesions, *Strongyloides stercoralis,* will be discussed later.

The second feature of this patient's illness is leukoerythroblastosis, the presence on the peripheral blood smear of nucleated erythrocytes and immature neutrophils ordinarily seen only in the bone marrow. In three studies comprising nearly 300 patients many causes of leukoerythroblastosis were found (Table 3).[17-19] The most frequent underlying mechanism is bone marrow infiltration by malignant cells or abnormal stem cells related to the myeloproliferative disorders, such as myeloid metaplasia or polycythemia vera. There is no evidence of these diseases in this patient. Although leukemia is associated with Gram-negative bacteremia and hemorrhage, these usually occur from neutropenia and thrombocytopenia, respectively, neither being present in this case. An occult malignant disorder is possible, especially because the impaired immune surveillance associated with renal transplantation enhances the risk of certain neoplasms.[20] The increased incidence of cancer, however, does not include common malignant tumors of the general population, such as of lung, prostate, breast, colorectal or uterine cervix. Prostate cancer and breast cancer, in fact, are the malignant disorders most likely to cause leukoerythroblastosis. Skin cancer, mainly squamous cell, occurs from 4 to 20 times more frequently in renal transplant recipients than in the general population, but the lesions are localized, easily discerned and readily controlled.

TABLE 3.—*Causes of Leukoerythroblastosis**

Marrow Infiltration	(56%)	Hemolysis	(8%)
Carcinoma	12%	Infections	(7%)
Acute leukemia	11%	Miscellaneous	(29%)
Lymphoma	10%	Gastrointestinal tract hemorrhage	4%
Myeloid metaplasia	8%	Renal transplant	2%
Chronic leukemia	8%		
Preleukemia	3%		
Multiple myeloma	2%		
Polycythemia vera	2%		

*Data were compiled from three clinical studies.[17-19] Numbers in parentheses represent the percent of patients falling into each category.

Lymphomas occur frequently in renal transplant recipients, but do not follow the usual histologic distribution. Whereas Hodgkin's disease ordinarily represents 34% of all lymphomas, it constitutes only 3% of those in renal transplant patients.[20] Non-Hodgkin's lymphomas, however, occur 45 to 100 times more frequently in renal transplant recipients than in the general population. The average patient age is 38, the male-to-female ratio is 2:1 and the mean time following transplantation is 30 months. The patient in the case discussed here received his graft about 16 months before his current illness, which is within the range reported. Of patients with lymphoma 40% have central nervous system involvement, and most other patients have peripheral lymphadenopathy. However, neither was evident in this patient. A lymphoma involving the small bowel and causing bleeding and perforation is possible, but the chest roentgenographic abnormalities would be difficult to explain.

The other malignant disorder whose incidence is increased in renal transplant recipients is Kaposi's sarcoma, which accounts for 3.3% of cases of cancer in this group compared with 0.6% in the general population. About 60% involve the skin or oropharyngeal mucosa only, while 40% affect the viscera, especially the alimentary and respiratory tracts. Skin or oropharyngeal lesions are almost always present, however, typically as reddish-brown or purplish nodules. Their

TABLE 4.—*Pulmonary Infections in Patients With Defective Cellular Immunity*

Organisms	
Bacteria	Viruses
Salmonella	Herpes simplex
Legionella	Varicella-zoster
	Cytomegalovirus
Higher Forms of Bacteria	
Nocardia	Parasites
Mycobacteria	*Pneumocystis carinii*
	Strongyloides stercoralis
Fungi	
Cryptococcus neoformans	
Aspergillus	
Mucor	
Candida	

absence makes this diagnosis unlikely. Because an occult malignant lesion appears improbable, a review of the other causes of leukoerythroblastosis suggests that infection, gastrointestinal hemorrhage or renal transplantation itself might explain the hematologic abnormalities in this patient.

The last area to examine is the presence of diffuse pulmonary infiltrates in this immunocompromised host. In general, it is useful to divide the diagnostic possibilities into four categories: (1) the underlying disease itself; (2) a direct effect of the treatment, either an adverse drug reaction or pneumonitis from radiation therapy; (3) infection, and (4) miscellaneous causes, especially pulmonary hemorrhage, edema or emboli. Pulmonary infection appears obvious, but the roentgenographic pattern makes conventional types of Gram-negative bacillary pneumonia unlikely, as they are usually focal processes, even in an immunodeficient host. There are three possible explanations for the concurrence of the Gram-negative rods in both blood and sputum: (1) the bacteremia arises outside the lung, the pulmonary process is unrelated and the organism's presence in the sputum represents colonization, not infection; (2) the lung is the primary source of the bacteremia, but the organism is unusual; (3) a Gram-negative bacillary pneumonia is superimposed on another pulmonary process. The first possibility seems highly improbable. Among unusual Gram-negative rods, *Salmonella* could explain the gastrointestinal hemorrhage and a concomitant pneumonia. *Salmonella* usually causes a focal infiltrate, however. A miliary pattern has been described,[21] but a mixed interstitial-alveolar appearance rarely, if ever, occurs.

The most likely explanation is a Gram-negative bacillary pneumonia accompanying another infection. The infections to consider are those regulated by cell-mediated immunity (Table 4), most of which have been discussed already. Cytomegalovirus, however, deserves careful scrutiny. It can cause a diffuse mixed alveolar-interstitial pneumonia that is often complicated by Gram-negative superinfections, and it has been isolated from intestinal ulcers that may bleed. Cytomegalovirus pneumonia tends to occur in the first few months after transplantation, however, and bacterial infections typically develop because of the neutropenia that the cytomegalovirus infection often induces.[22] These points make the diagnosis of cytomegalovirus unlikely. *Pneumocystis carinii* can cause a pneumonia like this patient's, but bacterial superinfection is uncommon without neutropenia, and this parasite does not involve the intestinal tract.

The remaining organism to consider, *Strongyloides stercoralis,* provides the best explanation for this patient's illness. A review of the life cycle of this worm will explain how it could persist for 30 years after the patient left an endemic area. *S stercoralis* is present throughout the tropics, where it is free-living in the soil as infective filariform larvae.[23] These larvae enter the skin and, via the lymphatic and venous circulations, migrate to the lung, whence they are expectorated and swallowed. In the upper intestinal tract they mature into adult worms and reproduce to yield noninfective progeny called rhabditiform larvae. These leave the gastrointestinal tract in feces and mature in soil to become the infective filariform larvae. Some rhabditiform larvae transform into the invasive filariform stage while still in the intestinal tract and can then traverse the bowel wall or perianal skin to reinfect the host. This "autoinfection" is especially likely to occur when decreased gastrointestinal motility prolongs the larval transit time in the alimentary canal or abnormalities such as colonic diverticula provide areas of stasis where larvae can mature. Autoinfection is common in normal hosts, allowing the parasite to persist for decades. In a follow-up study of 160 Australian prisoners in Southeast Asia during World War II, 27.5% had *Strongyloides* infection 34 to 37 years after leaving the endemic area.[24]

Autoinfection occurs especially in immunocompromised hosts, primarily in those receiving high-dose systemic corticosteroids. In these patients the larvae can enter the bloodstream in such great numbers that overwhelming strongyloidiasis develops.[25,26] The primary clinical manifestations involve lung, gastrointestinal tract and skin. Larvae in the lung cause dyspnea, cough, wheezing, purulent sputum, hemoptysis and diffuse infiltrates with a mixed alveolar-interstitial pattern. These helminths can cause diarrhea, small and large intestinal tract ulcers that may bleed and upper abdominal pain similar to that of peptic ulcer disease. As the filariform larvae penetrate the skin, usually in the perineal and thigh area, they can cause pustules or a serpiginous lesion known as larva currens, which outlines the larval migration.

About 45% of cases of overwhelming strongyloidiasis are associated with superinfections with enteric bacteria, usually Gram-negative bacilli like *Escherichia coli* and *Klebsiella.* Bacteremia, pneumonia and meningitis, alone or in varying combinations, may occur. Parasitologists have proposed the following three theories to explain the bacteremia: (1) disruptions of the bowel wall allow enteric organisms to enter the bloodstream; (2) the bacteria adhere to the external surfaces of the larvae as they enter the circulation, and

Figure 2.—Sputum cytology specimen examined by light microscopy (reduced from magnification ×40) shows two helminth larvae.

(3) larvae traveling in the bloodstream excrete bacteria from their alimentary canals. The diagnosis of overwhelming strongyloidiasis is established by finding filariform larvae in specimens of sputum, feces or, occasionally, cerebrospinal fluid.[27,28] Although blood eosinophilia is characteristic of strongyloidiasis in a normal host, the eosinophil count is usually normal or reduced in patients with overwhelming disease.

The treatment of this disorder is one of the few cases in medicine where the Mae West approach is appropriate. It was Mae West who said, "Too much of a good thing is . . . wonderful." In the world of helminthology this means more thiabendazole. For immunocompetent hosts, thiabendazole given orally in doses of 25 mg per kg of body weight twice a day for two days cures intestinal *Strongyloides* infestation. Immunosuppressed patients, however, require at least five days of treatment and often much longer before the infection is eradicated.[29] Even with thiabendazole and appropriate therapy of any concomitant bacterial process, however, the death rate for overwhelming strongyloidiasis in compromised hosts is about 40%.[25]

A review of the problem list (Table 1) shows how strongyloidiasis can explain the present patient's illness. The multiple pustules and cutaneous abscesses, especially in the perineal and thigh area, may represent autoinfection with filariform larvae. The gastrointestinal hemorrhage, abdominal pain, anemia and hypoalbuminemia may be due to intestinal ulceration with fecal loss of blood and protein. Although the duodenal ulcer seen on radiographs may have been peptic in origin, it might also be an example of strongyloidal ulceration. The presence of colonic diverticula may have permitted transformation of the larvae from the rhabditiform to the filariform stage, allowing the organism to persist for years. The raised serum amylase level may represent decreased amylase excretion because of renal insufficiency or the unexplained elevation seen in some patients following renal transplantation.[30] Alternatively, however, *Strongyloides* larvae can disseminate hematogenously to the pancreas, where they cause inflammation. The wheezing, dyspnea, fever, purulent sputum, hemoptysis and diffuse pulmonary infiltrates are probably due to larvae in the lung and the complicating Gram-negative pneumonia with bacteremia.

JAMES J. PLORDE, MD:* A cytologist rather than a parasitologist provided the answer to this patient's puzzling illness. With the worsening of the patient's respiratory state, sputum specimens were collected and sent to the pathology department for cytologic examination. Among the normal host cells lay a most unusual structure identified as a helminth larva (Figure 2). This finding led, in search of a more definitive identification, to an examination of the patient's stool specimens. Numerous rhabditiform, or free-feeding, helminth larvae were found. Only one common intestinal helminth, *S stercoralis,* regularly deposits such larvae in feces, making the diagnosis of disseminated strongyloidiasis likely. Occasionally, however, eggs of other helminth species, especially hookworm, if present in a stool specimen and allowed to embryonate for several hours in a warm laboratory, can hatch, releasing larvae morphologically similar to *Strongyloides.* To distinguish between these larvae one must closely inspect the buccal cavity and genital primordium of the worm in question. The hookworm larvae have a larger buccal cavity and a smaller genital primordium. The larvae found in the stool specimen of this patient had a short buccal cavity and large genital primordium, establishing them as *Strongyloides* larvae.

As Dr Hirschmann mentioned in his discussion, disseminated strongyloidiasis occurs when the noninvasive rhabditiform larvae generally found in feces molt into the larger and invasive filariform stage. Thus, the diagnosis of disseminated strongyloidiasis usually rests with the finding of the forked-tail filariform larvae in feces or sputum. On careful examination of the stool specimen these forms were found, making a conclusive diagnosis of overwhelming strongyloidiasis. The Gram-negative bacillus present in the blood and sputum was *Klebsiella.* With appropriate antibiotic therapy and several days of thiabendazole treatment, his bacterial and parasitic infections resolved. Several months later, he has continued to do well, with no evidence of recurrent strongyloidiasis.

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Medical Staff Conference

The Design of Rational Combination Chemotherapy for Cancer

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Cancer is an extraordinarily important group of diseases not only because of the statistics of mortality, but because of the special dread that it often elicits. Peyton Rous, who won a Nobel prize for his pioneering work concerning viruses and cancer, wrote as follows: "Tumors destroy man in an unique and appalling way, as flesh of his own flesh, which had somehow been rendered proliferative, rampant, predatory and ungovernable." Fortunately there has been remarkable progress in the treatment of various cancers over the past generation. Much of this has been based on empirical studies, but increasingly these therapeutic protocols are being based on considerations that will be described in this Medical Staff Conference.*

Our speaker will be Dr Edwin C. Cadman, Professor of Medicine and Director of the Cancer Research Institute. Dr Cadman joined our faculty in the above capacity only a few months ago following a distinguished career in oncology at Yale.

General

DR CADMAN:† Cancer is the second leading cause of death in this country, exceeded only by deaths due to heart disease. About 440,000 people will die of cancer this year, and there will also be 1.2 million new cases of cancer diagnosed.[1] Although these numbers appear somewhat discouraging, it is estimated that this year about 50,000 patients will be cured of their cancer by the use of chemotherapy.[2] Cure is defined as achieving a state wherein chemotherapy can be discontinued after a maximum of six months of treatment and the patient can return to a normal and productive life expectancy without further need for treatment. The only other diseases that an internist can cure with medication as just defined are the infectious diseases. The unfortunate nature of these curable cancers, however, is that they comprise less than 10% of the total number of cancers diagnosed in this country (Table 1). The one major difference that separates these curable cancers from the noncurable cancers, such as lung cancer, colon cancer, cancer of the pancreas and the other more common neoplastic diseases, is that the curable cancers tend to have doubling times of about 30 to 60 days.

Most of the drugs that are available for current use by oncologists were developed 15 or 20 years ago, some as many as 25 to 30 years ago. These drugs were designed primarily to interfere with DNA synthesis because at the time of their development normal DNA structure and function were considered the most crucial requirement for cell division and therefore tumor growth. This knowledge helps explain why most of the current antineoplastic agents are most effective in rapidly proliferating tumors. In fact, all of these drugs were screened against and were required to kill rapidly proliferating mouse leukemia and lymphoma cells that had doubling times of 12 hours. Current drug development concepts involve the creation of agents that may have selective activity against cancer cells compared with normal cells. This novel approach to the design of newer antineoplastic drugs is permissible because malignant cells often contain unique cellular proteins and occasionally different quantities of cell surface antigens. Even the older drugs, if attached to monoclonal antibodies specific for different antigenic substances on malignant or transformed cells, could theoretically de-

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†Edwin C. Cadman, MD, Professor of Medicine; Director of the Cancer Research Institute, and Chief, Oncology and Hematology.

(Cadman EC: The design of rational combination chemotherapy for cancer—Medical Staff Conference, University of California, San Francisco. West J Med 1984 Jun; 140:921-928)

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ABBREVIATIONS USED IN TEXT

dTMP = deoxythymidylate
dTTP = deoxythymidine triphosphate
dUMP = deoxyuridylate
FdUMP = fluorodeoxyuridylate
FdUTP = fluorodeoxyuridine triphosphate
FH_2 = dihydrofolate
FH_4 = tetrahydrofolate
5-FU = 5-fluorouracil
FUMP = 5-fluorouridylate
FUTP = 5-fluorouridine triphosphate
HGPRTase = hypoxanthine-guanine phosphoribosyltransferase
OPRTase = orotate phosphoribosyltransferase
PRPP = 5-phosphoribosyl-1-pyrophosphate
TMP = thymidylate (thymidine monophosphate)
TTP = thymidine triphosphate
UMP = uridylate (uridine monophosphate)
UTP = uridine triphosphate

liver the toxic agent selectively to the desired site. These are purely concepts, however, that remain to be developed and evaluated. The issue an oncologist must consider is how to optimally treat a patient whose cancer is diagnosed today.

Chemotherapy for malignant disease is the result of medical knowledge that was accumulating in the 1940s. Infectious diseases were finally being cured with antibiotics. This provided a major impetus for the development of drugs to cure cancer. In addition, the DNA structure was being identified, and the precise nature of its activity was found to be crucial to cellular proliferation. Therefore drugs that interfered with this nucleic acid were thought to have particular interest as anticancer drugs. What was not appreciated then was that cancer cells were more like normal cells than they were different, and this selective destruction of malignant cells was not often achieved. The excitement that followed antibiotic treatment of bacterial disease was replaced by disappointment when toxic effects on normal tissue became dose limiting after drug treatment for cancer was introduced.

Mechlorethamine hydrochloride, a nitrogen mustard, was the first drug used, in 1943, to treat patients who had Hodgkin's disease, after it had been documented that lymph nodes disappeared in soldiers exposed to mustard gas.[3] The result was a dramatic size reduction of cancerous lymph nodes, the duration of which was only temporary. In 1947 it was established that administration of the antifolate, methotrexate, could result in rapid elimination of leukemic lymphocytes in children with acute lymphocytic leukemia.[4] In 1955 this same drug was associated with the first cures in women who had gestational choriocarcinoma.[5] With the aforementioned theoretical reasoning and with these successes, chemotherapy for malignant disease seemed a very worthwhile endeavor.

Drug development has been a laborious and time-consuming process. This effort is sponsored primarily by the National Cancer Institute, though recently the pharmaceutical industry has been investing in drug research processes. Over the past 20 years, 700,000 agents have been screened for possible chemotherapeutic use under the direction and funding of the National Cancer Institute.[2] These include 350,000 compounds that were synthesized, some for the specific purpose of interrupting cellular metabolism. About 200,000 were obtained from fermentation products and about 120,000 extracts of plant products were tested. The remaining compounds were simply miscellaneous agents. The process of drug acquisition requires a uniform screening procedure before the drugs can become available to treat patients. Drugs must be evaluated in test tube systems against several cultured malignant cell lines. If a drug shows some inhibitory activity against these tumor cells, it is then tested in small rodents containing tumors. It these tumors are successfully treated with the agent, then the drug is produced in sufficient quantities to allow toxicology testing to be done in large animals. Once the toxicology is understood, the drug is eventually allowed to be used in clinical trials.

TABLE 1.—*The Curable Cancers**

Cancer in Adults	*% Cured*	*Cancer in Children*	*% Cured*
Hodgkin's disease	80	Acute lymphocytic leukemia	60
Diffuse histiocytic lymphoma	50	Embryonal rhabdomyosarcoma	80
Nodular mixed lymphoma	50	Burkitt's lymphoma	50
Testicular carcinoma	80	Wilms' tumor	80
Gestational choriocarcinoma	80	Ewing's sarcoma	70
Ovarian carcinoma	10		
Acute myelogenous leukemia	10		

*From "Cancer Statistics 1984"[1] and Frei.[2]

The clinical testing program has the following three phases: Phase I is the use of these agents in patients who have a malignant tumor and in whom either standard therapy has failed or for whom no therapy exists. The disease is required to be far advanced and a patient's life expectancy to be less than two months. This study is specifically designed to learn the effects of these drugs –primarily their toxicity—on humans. The goal is to determine the safe drug dose for humans. During this particular phase, pharmacokinetic evaluations are often done and the dose and timing of drug administration estimated. Because of the escalating nature of dose administration in these clinical studies, only about 15 to 20 patients are required to establish a reasonably safe drug dose. The far-advanced nature of the cancer in these patients precludes evaluating these agents for therapeutic efficacy during this phase of clinical testing.

Phase II clinical evaluation is to identify the potential therapeutic usefulness of the new agent. Similar patients are selected for these studies as were for the phase I trials, with the exception that their life expectancy should be about six months or longer. Patients are administered drug doses that were selected in the phase I trial to be safe. Repeated treatments are given, with the primary objective being the documentation of

TABLE 2.—*Chemotherapeutic Drug Classification*

Alkylating Agents	
Cyclophosphamide	Lomustine (CCNU)
Melphalan	Semustine (methyl CCNU)
Busulfan	Streptozocin
Carmustine (BCNU)	Cisplatin
Antimetabolites	
Methotrexate	5-Azacitidine
5-Fluorouracil	Cytarabine
6-Mercaptopurine	Hydroxyurea
6-Thioguanine	
Antibiotics	
Doxorubicin hydrochloride	Bleomycin sulfate
Daunorubicin hydrochloride	Dactinomycin
Mithramycin	
Plant Alkaloids	
Vincristine sulfate	Etoposide (VP-16-123)
Vinblastine sulfate	
Miscellaneous	
Procarbazine hydrochloride	Hexamethylmelamine
Dacarbazine (DTIC)	L-Asparaginase

tumor responses. Drugs should be tested in all tumor types, but this is impractical. Drugs are often tested in only about five to ten common tumor types—lung cancer, ovarian carcinoma and breast cancer. In the phase III clinical trial, the new drug therapy is compared with the standard therapy for that particular cancer that responded to the new drug in the phase II testing. This last phase of clinical testing is often a randomized study.

This entire acquisition, screening and clinical testing program can take, on the average, about ten years. Therefore, drugs that are currently being developed will not be available for routine clinical use until the mid-1990s. These clinical cancer trials require the commitment of a compassionate physician, for often the best that can be offered to those willing patients is empathy and hope.

The common available chemotherapeutic antineoplastic agents are listed in Table 2. There are about 50 agents available for use in the treatment of cancer, including experimental drugs and hormones. It is well established that combination drug therapy for cancer almost always results in a higher response rate. In fact, all of the cancers listed in Table 1 are curable with combination therapy (to the percentages indicated only). Therefore, it is reasonable and appropriate to believe that combination therapy is better for achieving tumor responses, long-term remissions and cures in cancer patients. The problem is, of course, deciding the best and most logical method by which to select a drug combination. The following are often considered during this drug selection process: tumor cell kinetics and cell cycle activity of the drugs (use drugs that interfere with DNA synthesis if the tumor is growing quickly), mechanisms of drug resistance (do not use drugs that act at the same enzyme site or use the same carrier protein to enter the cell) and host toxic reactions (do not use drugs with the same toxicity). The major choice of drugs for use in combination therapy is, unfortunately, arbitrary or random. This capricious approach to the design of cancer therapy is in need of gentle direction. If there are 50 drugs from which to select a three-drug combination, nearly 20,000 different drug combinations can be randomly chosen. This large figure does not include varying the drug dose or frequency of drug administration. A random, unscientific approach to the design of drug combination cancer treatment could overwhelm the capacity of our academic centers, resulting in chaos and eventually in disappointment.

Biochemical Modulation

A more scientific approach to selecting drug combinations should be attempted to avoid the confusion and dismay that result from random choice. Biochemical modulation is a rational method of selecting drugs for combination trials. The effect of one drug on the intracellular metabolism and the consequence of these perturbations on a second drug constitute the foundation of the principles of biochemical modulation. Our research laboratory has been investigating the interaction of methotrexate and 5-fluorouracil (5-FU) to determine biochemically the most rational way to combine these two agents. These drugs were chosen for evaluation for two reasons. The first was that they were antimetabolites that affected nucleotide metabolism and therefore would be capable of being modulated within cells by alterations in intracellular nucleotide levels. The second was that these drugs are perhaps the two most common drugs used for treatment of the most common and incurable cancers: cancer of the colon and the breast. Our studies have shown that when methotrexate is given before 5-FU, enhanced intracellular accumulation of 5-fluorouracil occurs, which is associated with synergistic killing of cancer cells. The following is an explanation of this drug interaction that shows how basic laboratory information can be of use in the design of clinical treatment.

Interaction of Methotrexate and 5-Fluorouracil

Effect of Methotrexate

Methotrexate is an antifolate drug that inhibits the enzyme dihydrofolate reductase. The consequence of this inhibition is the prevention of the regeneration of the biologically active tetrahydrofolate (FH_4) from the biologically inactive dihydrofolate (FH_2). Deoxythymidylate (dTMP), the precursor of deoxythymidine triphosphate (dTTP), one of the four nucleoside triphosphates required for DNA synthesis, is created simply by the transfer of the methyl group from the folate, 5,10-methylenetetrahydrofolate, to deoxyuridylate (dUMP). This methyl group to be donated to dUMP is carried by the tetrahydrofolate structure, which loses two hydrogens during the transfer process, leaving the biologically inactive oxidized dihydrofolate (Figure 1). Therefore, when dihydrofolate reductase is inhibited by methotrexate, the synthesis of dTMP from dUMP consumes the FH_4 by converting it to FH_2, which can no longer be converted back to the active

FH_4.[6] When the FH_4 levels are reduced below concentrations that will support the synthesis of dTMP, then DNA synthesis ceases. Obviously, methotrexate would only be effective in cells that required dTTP, or are synthesizing DNA.

Intracellular folates are also necessary for one-carbon metabolism in the de novo purine synthetic pathway. The formation of formylglycinamide ribonucleotide from glycinamide ribonucleotide requires 5,10-methenyl FH_4. The synthesis of 5-formaminoimidazole-4-carboxamide ribonucleotide requires the transfer of the formyl group from 10-formyl tetrahydrofolate to 5-aminoimidazole-4-carboxamide ribonucleotide. Neither one of these folate-requiring steps results in the oxidation of the FH_4 structure to the biologically inactive FH_2 derivative. Therefore, the FH_4 compound that results after the one-carbon transfer during purine synthesis can obtain other one-carbon units required for further purine synthesis without the requirement of the enzyme dihydrofolate reductase. The presumed effect of methotrexate on the purine synthetic pathway is thus an indirect one and the consequence of the altered folate pools that result from continued dTMP synthesis in the presence of dihydrofolate reductase inhibition. When dihydrofolate reductase is inhibited by methotrexate, $K_i \simeq 10^{-11}$ M[7]; 5,10-methylene FH_4 is utilized by the conversion of dUMP to dTMP, producing FH_2 until the folate cofactor, 5,10-methylene FH_4, can no longer support this reaction at a rate that sustains DNA synthesis. Presumably a sufficient amount of FH_4, which would have undergone conversion to 5,10-methenyl FH_4 or 10-formyl FH_4 for purine synthesis, is now transformed to 5,10-methylene FH_4 in an attempt to continue the synthesis of the needed dTMP. The response to the inhibition of dihydrofolate reductase by methotrexate therefore results in a reduction in de novo purine synthesis because of this continued use without replenishment of FH_4 (Figure 2). The influence of methotrexate on the synthesis of purines had been appreciated in 1958[8]; however, the cytotoxic effect of methotrexate was always considered the result of a thymineless state.[9,10]

The following experimental evidence substantiates the validity of this effect of methotrexate on purine synthesis. Glycine is normally incorporated into the purine ring during formation of the purine structure glycinamide ribonucleotide from phosphoribosylamine. Glycine, which has a ^{14}C label at the 1 position of the molecule, can be used to measure the rate of purine synthesis. In unperturbed cell growth the 1-^{14}C label can be found in the purine nucleotides that are incorporated into DNA and RNA. However, in the presence of methotrexate at concentrations that inhibit dihydrofolate reductase maximally for at least one cell doubling time, the ^{14}C label was substantially reduced in these purine nucleotides, indicating a reduction in the new synthesis of adenine and guanine, the purines. This observation is consistent with the proposed indirect inhibition of de novo purine synthesis by methotrexate (Figure 3).[11]

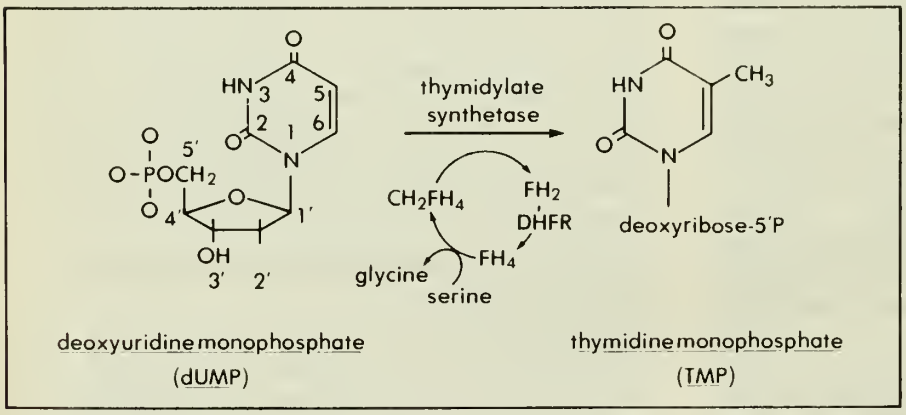

Figure 1.—The conversion of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (TMP). Deoxyuridylate, or dUMP, obtains a methyl group in the 5 position of the base ring from the folate, 5,10-methylenetetrahydrofolate (CH_2FH_4). The result is TMP and the oxidized folate, FH_2. This latter folate is inactive and must be converted to tetrahydrofolate (FH_4) to sustain further TMP synthesis. DHFR = dihydrofolate reductase

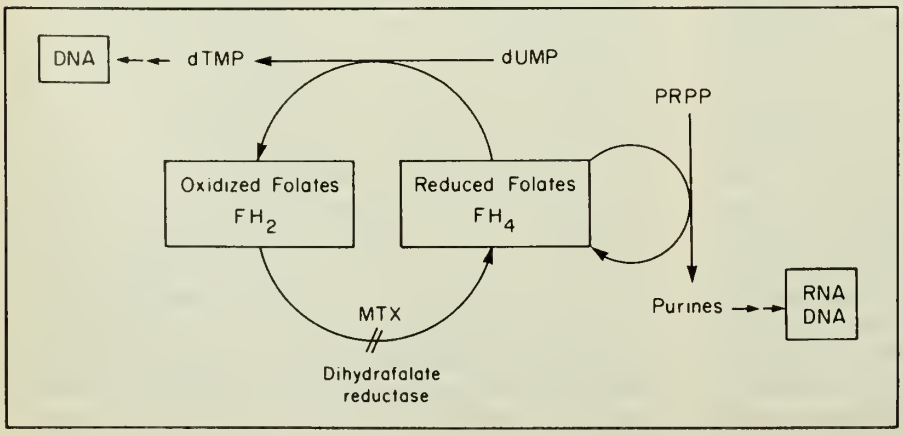

Figure 2.—The mechanism by which methotrexate (MTX) affects intracellular folate levels. Normally the reduced folates (FH_4) carry one carbon group to the de novo purine synthetic pathway and return unaltered to the FH_4 pool. When the FH_4 moiety transfers a carbon group to deoxyuridine monophosphate (dUMP), forming thymidylate (dTMP), the FH_4 loses two hydrogens (is oxidized). This biologically inactive folate (FH_2) must obtain two hydrogens (be reduced) by dihydrofolate reductase (DHFR). PRPP = phosphoribosylpyrophosphate

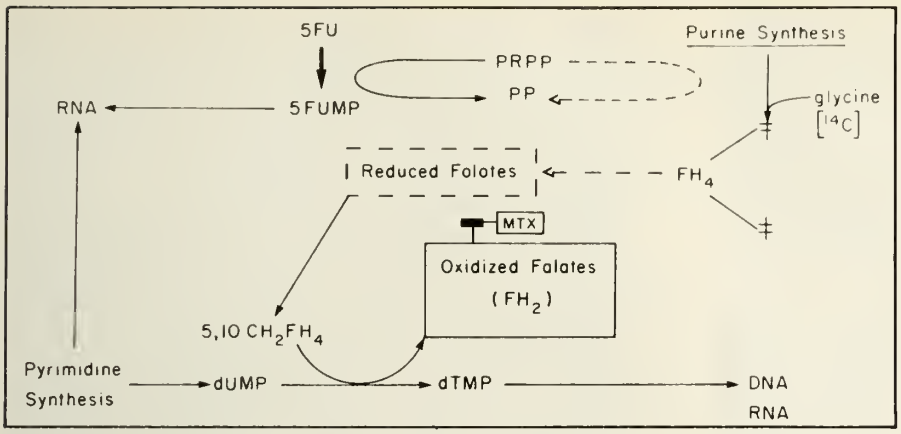

Figure 3.—The mechanism by which methotrexate (MTX) results in enhanced intracellular accumulation of 5-fluorouracil (5-FU). When methotrexate inhibits dihydrofolate (FH_2) reductase, FH_2 cannot be converted back to the biologically active tetrahydrofolate (FH_4). Consequently, purine synthesis ceases, phosphoribosylpyrophospate (PRPP) increases, which in turn can be used for the metabolic conversion of the base, 5-FU, to the nucleotide derivative, 5-FUMP. PP = pyrophosphate, 5,10-CH_2FH_4 = 5,10-methylenetetrahydrofolate, dTMP = thymidylate, dUMP = deoxyuridylate

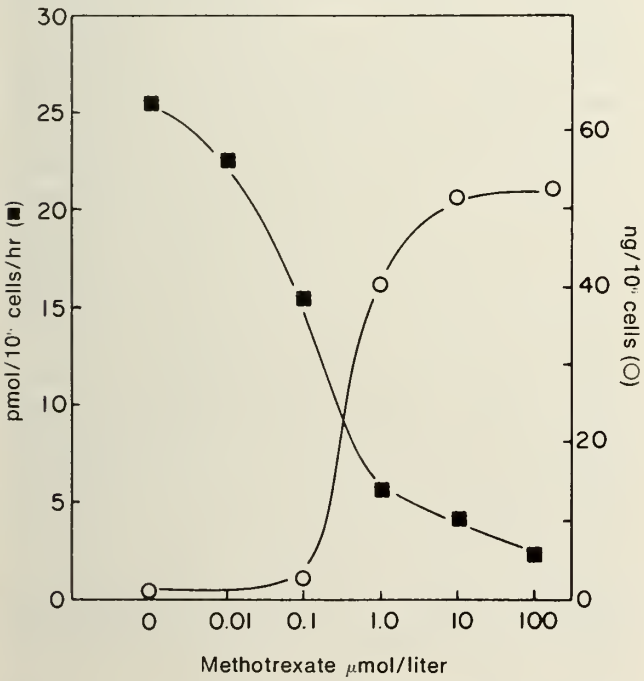

Figure 4.—The effect of increasing methotrexate concentrations for a six-hour exposure on the synthesis of purine bases and phosphoribosylpyrophosphate (PRPP) levels in L1210 mouse leukemia cells. Single cell suspensions of L1210 cells were exposed to the indicated concentration of methotrexate. After six hours the amount of radiolabeled glycine that accumulated into adenine and guanine over two hours was determined. Simultaneous determinations of PRPP were also done. ○ = PRPP, ■ = 1-^{14}C-glycine into adenine and guanine

The consequence of this inhibition on the de novo purine pathway is an increase in the availability of 5-phosphoribosyl-1-pyrophosphate (PRPP), which normally contributes the phosphoribosyl moiety with the amino group donated by glutamine to form phosphoribosylamine. This is the first enzymatic process in the synthesis of purines. The PRPP can also be used by orotate phosphoribosyltransferase (OPRTase), an enzyme used in the de novo pyrimidine synthetic pathway, as well as by hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) and adenine phosphoribosyltransferase (APRTase), enzymes used in the salvage of purines. In each enzymatic conversion, the phosphoribosyl moiety of PRPP is combined with the respective base. For example, HGPRTase can only utilize hypoxanthine or guanine. The activity of these enzymes can be influenced by the availability of their obligatory cosubstrate, PRPP, and the base to be converted to a nucleotide. 5-Fluorouracil is a base analog of uracil and requires PRPP for activation or conversion to the nucleotide fluorouridylate (FUMP). Therefore 5-FU activation can be influenced by an increase in PRPP levels, which can be achieved following methotrexate treatment. In Figure 4 is shown that in L1210 mouse leukemia cells, as the concentration of methotrexate is increased over an exposure of six hours, there is a resultant decrease in the amount of radiolabeled glycine in the purines. This reduction in purine synthesis in response to methotrexate is accompanied by a concomitant increase in the intracellular concentrations of PRPP.

The Enhancement of 5-Fluorouracil Accumulation in Cancer Cells by Methotrexate

5-Fluorouracil is identical to uracil, except that on the 5 position of the 6-membered pyrimidine ring there is a fluorine atom; this is precisely where the methyl group was to have been placed during dTMP synthesis (Figure 1). 5-Fluorouracil enters the cells by facilitated diffusion and then is converted to the monophosphate nucleoside, FUMP (Figure 3). The mechanism by which 5-FU kills cells will be discussed later.

The conversion of 5-FU to 5-fluorouridylate (FUMP) is by OPRTase. This initial ribosylphosphorylation is considered to be rate limiting in the total intracellular accumulation of 5-FU ribonucleotide derivatives and therefore the important enzymatic process that could be modulated. This enzyme, which activates 5-FU, requires PRPP from which the phosphoribosyl moiety is transferred to 5-FU to form FUMP. It is from this monophosphate derivative of 5-FU that the subsequent formation of other 5-FU nucleotides occurs.

After methotrexate exposure and the elevation of PRPP levels, 5-fluorouracil can be converted in greater quantity to FUMP by OPRTase. When methotrexate was given to L1210 cell cultures at concentrations that saturated dihydrofolate reductase, generally greater

than 1 μmol per liter, deoxythymidine triphosphate (dTTP) pools were reduced, purine synthesis was inhibited and PRPP levels increased fivefold to tenfold (7 ng per million cells to 52 ng per million cells after a three-hour exposure to methotrexate). When 5-FU was added to these methotrexate-exposed cells, the rate and total intracellular accumulation of 5-FU metabolites increased fivefold.[11-13] The biological significance of this enhanced 5-FU accumulation in methotrexate-pretreated cells was synergistic cell killing.

Important factors that can influence this biochemical modulation between methotrexate and 5-FU are the dose of methotrexate, the interval between the administration of methotrexate and that of 5-FU, the population of tumor cells undergoing DNA synthesis and the presence of other compounds that could use and therefore consume PRPP. For example, FH_4 depletion will occur only in cells exposed to methotrexate that are synthesizing dTMP and therefore utilizing 5, 10-methylene FH_4. Hypoxanthine is also a base that is converted to inosine monophosphate in the presence of PRPP by HGPRTase. The inosine monophosphate enters the purine pathway beyond where the folate carbon transfers are required for purine synthesis. Therefore hypoxanthine can both use PRPP and sustain the production of adenine and guanine in the presence of methotrexate. Consequently, cells exposed to high concentrations of hypoxanthine after methotrexate treatment will not accumulate large quantities of 5-FU nor will there be synergistic cytotoxicity. This has clinical implications because some patients have sufficient serum concentrations of hypoxanthine to blunt the biochemical modulatory effects described. Allopurinol, an analog of hypoxanthine that also requires PRPP for activation and, in addition, will increase hypoxanthine serum levels, has the potential to completely inhibit the conversion of 5-FU to its active derivatives. Finally, leucovorin, which is an exogenous source of FH_4, will rapidly reverse the effects of the methotrexate inhibition on dihydrofolate reductase. If leucovorin is administered after the methotrexate but before 5-FU, the intracellular biochemical alterations described and enhanced cytotoxicity of the methotrexate/5-FU sequence will also be totally abrogated.

The sequential administration of methotrexate before 5-FU was initially studied in L1210 cells. Similar modulation of 5-FU metabolism and enhanced cytotoxicity has also been observed in the human colon carcinoma cell line HCT-8 and the human breast cancer cell line 47-DN.[13,14] In Figure 5 the results of these studies in human breast cancer cells are summarized. Although the maximum effect on 5-FU metabolism—PRPP elevation—and cytotoxicity of sequential methotrexate and 5-FU administration occurred between three and six hours for the L1210 cells, the optimal methotrexate exposure duration to potentiate 5-FU accumulation for the human breast cancer cell line occurred after 24 hours. Knowing this duration of methotrexate exposure for the maximum effect on 5-FU activation and cytotoxicity is important when this information is being used to design sequential therapy for cancer patients. The most obvious reason for this difference required for optimal biochemical modulation is that the L1210 cells have a 12-hour doubling time, whereas the human cells have a doubling time of 24 to 36 hours. As previously noted, methotrexate is maximally effective in cells that are actively synthesizing DNA (making dTMP). Therefore, the longer the exposure to methotrexate of a slowly dividing cell population, the greater is the proportion of the total cell population that will begin to synthesize DNA and be affected by methotrexate. Other factors such as changes in methotrexate transport, polyglutamate formation of methotrexate and methotrexate retention may be related to growth patterns and may be

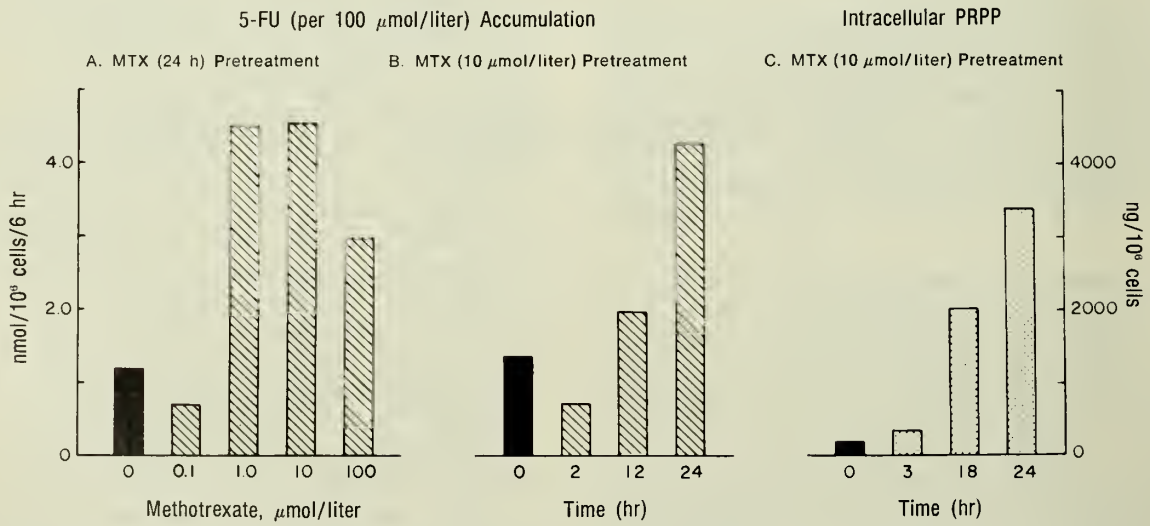

Figure 5.—The effect of methotrexate (MTX) concentration and duration of exposure to achieve maximum intracellular accumulation of 5-fluorouracil (5-FU) and elevation of phosphoribosylpyrophosphate (PRPP) levels were determined in the human breast cancer cell line, 47-DN. The optimal MTX concentration **(A)** was between 1 and 10 microns. After 24 hours of MTX, the PRPP levels **(C)** were maximum (longer MTX exposures were not better), which correlated with the maximum intracellular 5-FU accumulation **(B)**. ■ = no treatment, ▨ and □ = pretreatment as indicated

quite important as well.[15,16] Mechanisms by which cells can be synchronized or encouraged to undergo division (enter S-phase) could possibly enhance the sequential use of methotrexate and 5-FU. Estrogen stimulation of the breast cancer cell lines will, in fact, enhance the cytotoxicity of this drug sequence. Although the doubling time is decreased by estrogen treatment in breast cancer cells that contain estrogen receptors, other factors could be occurring.[17,18] This information was used to design a phase I clinical study in which methotrexate was given by mouth every six hours for five doses to sustain documented serum methotrexate concentrations in the specified range of 1 to 10 μmol per liter. After the 24-hour methotrexate exposure, an intravenous injection of a standard 5-FU dose was given. There was no severe toxic effect.[19]

Our current ongoing clinical trial involves an infusion of methotrexate (540 mg per sq m of body surface for 36 hours), with an infusion of 5-FU (1.5 grams per sq m) begun at 24 hours and continued for 24 hours. These drug doses were chosen to achieve blood concentrations similar to those found to be optimum for biochemical alterations and cytotoxicity as noted by laboratory studies—1 to 10 μmol per liter of methotrexate and 1 μmol per liter of 5-FU. For 12 hours (between the 24th and 36th hours), the methotrexate and the 5-FU infusions overlap. Leucovorin is given to patients beginning at the 36th hour. The therapy regimen is repeated every two weeks. Currently, 16 patients have been treated in this fashion after giving their informed consent. There have been minimal toxic effects. Therefore we plan on using this drug sequence for early treatment of metastatic breast cancer.

We are unable to state with assurance that this sequential therapy is selective for destroying cancer cells. We have evaluated normal bone marrow stem cells obtained from patients having a bone marrow biopsy done for other reasons. The methotrexate/5-FU sequence does not result in an enhanced destruction of bone marrow stem cells that develop into granulocyte or macrophage colonies (D. Armstrong, PhD, and E. Cadman, MD, unpublished observations, 1984). This may reflect the fact that the bone marrow environment contains hypoxanthine levels five to ten times greater than those found in serum (S. Howell, MD, University of California San Diego, unpublished observations, 1984). Therefore, perhaps the bone marrow has selective protection.

The Mechanism of Increased Cell Killing

The precise mechanism by which these two drugs result in enhanced cell killing is unknown but could be the consequence of several factors. The primary nucleotide forms of 5-fluorouracil considered to be cytotoxic are the analog of dUMP, fluorodeoxyuridylate (FdUMP), and the analog of uridine triphosphate (UTP), fluorouridine triphosphate (FUTP).

Inhibition of thymidylate synthesis. The conversion of dUMP to dTMP occurs by the enzymatic process of methyl transfer mediated by the enzyme, thymidylate synthetase. The fluoropyrimidine analog, FdUMP, binds tightly to this enzyme. This 5-FU derivative cannot receive a methyl group because at the 5 position of the ring where the methyl group is to be transferred, a fluorine atom exists. Because this nucleotide form of 5-FU is increased in cells pretreated with methotrexate, the mechanism of its cytotoxic action is important to understand. However, the binding of FdUMP to this enzyme is ordered and requires 5,10-methylene FH_4 for covalent bonding and enzyme inhibition to occur.[20] Therefore, in the presence of methotrexate, the 5,10-methylene FH_4 levels are depleted and the subsequent administration of 5-FU will not result in greater binding and inhibition of thymidylate synthetase by FdUMP. This is not the mechanism of enhanced cell killing.

Interaction with RNA function. The 5-FU ribonucleotide, fluorouridine triphosphate (FUTP), can be incorporated into newly synthesized RNA in place of UTP. The presence of FUTP in RNA does inhibit the processing of the larger nuclear RNA into appropriate smaller ribosomal RNA subunits. The higher molecular weight RNA normally undergoes cleavage at various sites, leaving RNA molecules of the correct size and structure that are then transported into the cytosol where they carry out their normal function. This processing occurs extensively to that nuclear RNA that subsequently becomes ribosomal RNA. When certain quantities (the exact amount is unknown) of FUTP are incorporated into the newly synthesized RNA strands, this processing is inhibited.[21,22] Methotrexate pretreatment does result in enhanced incorporation of FUTP into RNA; therefore, this may be a mechanism that could account for the enhanced cell killing following the methotrexate/5-FU sequence.

Interaction with DNA structure and function. The deoxynucleotide that is also made from 5-FU fluorodeoxyuridine triphosphate (FdUTP), can be incorporated into DNA in place of dTTP. The DNA polymerase can utilize FdUTP equally as well as it can dTTP. The amount of FdUTP incorporated into DNA depends on the ratio of FdUTP to dTTP. However, DNA does not contain uracil. The reason is that the enzyme, DNA-uracil glycosylase, acts quickly to remove any uracil. This in turn initiates the DNA excision repair process that ultimately replaces the site of the uridine nucleotide with dTTP.[23]

If large amounts of FdUTP are incorporated into DNA, the DNA repair process will function at such a rapid and efficient rate that the DNA will have many areas lacking bases (or have "holes") and therefore become nonfunctional. Under certain circumstances, this can lead to DNA fragmentation (E. Cadman, MD, unpublished observations, 1984). Some tumor cells may have enhanced DNA repair and therefore, in fact, be very susceptible to this injury. This mechanism could result in selective destruction of tumor cells com-

pared with normal nondividing cells under the right conditions.

Conclusion

Biochemical modulation as exemplified by the interaction of methotrexate and 5-fluorouracil can be used as a rational guide for the selection of drug combinations to be used in the treatment of cancer. In cells that are synthesizing DNA—that is, rapidly proliferating tumors—pretreatment with methotrexate results in enhanced intracellular accumulation of subsequently administered 5-FU. This enhanced intracellular 5-FU accumulation is the consequence of the antipurine effect of methotrexate and the resultant elevation of PRPP, which is the cosubstrate required for the metabolic conversion of the base, 5-FU, to the nucleotide, FUMP. The observed synergistic cell killing of the sequential administration of methotrexate and 5-FU is associated with this increased intracellular 5-FU nucleotide levels. Although the initial biochemical and cytotoxic studies were done in L1210 cells, they have been reduplicated in cultured human breast and colon cancer cells. This information does provide a rational basis from which to make therapeutic decisions when using methotrexate and 5-FU for cancer treatment.

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Epitomes

Important Advances in Clinical Medicine

Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in pediatrics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 44 Gough Street, San Francisco, CA 94103

Kawasaki Disease

KAWASAKI DISEASE (mucocutaneous lymph node syndrome), originally known by pathologists as infantile periarteritis nodosa, began to be recognized as a clinical entity in Japan and in the United States in the late 1960s. It has now been seen in most countries of the world, but it remains a disease of unknown cause that is increasing in incidence and that has a propensity to affect young children, especially those of Japanese or part-Japanese racial extraction. Cases have been diagnosed in more than 50,000 children of all races, and an unknown number remain unidentified.

The major clinical findings, described separately by Dr Kawasaki in Japan in 1967 and by Dr Melish in the United States in 1974, are fever lasting longer than five days and averaging 11 days in duration; conjunctival injection of blood vessels; changes of the mouth consisting of erythema of the lips followed by fissuring and crusting, diffuse reddening of the oropharynx and prominent papillae of the tongue ("strawberry" tongue), and involvement of the extremities including swelling of the hands and feet, reddening of the palms and soles, erythematous rash and lymphadenopathy. Also seen to a lesser degree are pyuria and urethritis, arthralgia and arthritis, aseptic meningitis, vomiting, diarrhea, abdominal pain, myocardiopathy, pericardial effusion, obstructive jaundice, hydrops of the gallbladder, acute mitral insufficiency and myocardial infarction. In recent years there have been patients who have not shown full-blown disease. Physicians need a high degree of awareness, using the five major criteria to arrive at a diagnosis.

Most of the patients are children 2 years old or younger, or are younger than 8 years of age. Boys outnumber the girls 1.5:1 in clinically recognized cases. These infants and young children are generally very ill and very irritable. Because they do not respond to antipyretic therapy or antibiotics (or both), they tend to be seen by their private physicians frequently during the first week of illness and are admitted to hospital because of a combined lack of response to therapy and the development of other signs and symptoms such as a rash or joint involvement.

Pertinent laboratory findings include an elevated leukocyte count during the febrile phase of more than 20,000 per μl with a shift to the left. The erythrocyte sedimentation rate and C-reactive protein are increased from the febrile phase for six to ten weeks. Other positive results often are small numbers of leukocytes in cerebrospinal fluid and in urine specimens, slightly elevated liver function values and occasional jaundice. Thrombocytosis occurs in all patients between the 15th and 25th day of illness, with a peak platelet count of 600,000 to 1.8 million per μl. This correlates with the period of acute coronary artery thrombosis.

This is a clinical disorder that is similar to a number of other childhood illnesses and, for this reason, the diagnosis is made only after other diseases have been ruled out. While the disease is self-limited within six to eight weeks in most cases, about 1.7% of patients will die of cardiac complications, including coronary artery aneurysms and thrombosis (most commonly), atrioventricular conduction abnormalities or, rarely, cardiac tamponade. Peripheral vasculitis is widespread throughout the body and affects large and medium-

sized musculoelastic arteries and, to a lesser degree, veins. The ratio of male to female patients in fatal cases is 3:1, and most are younger than 2 years of age at the time of death.

Special tests are required to diagnose coronary artery aneurysms, which affect about 20% of patients. Two-dimensional echocardiography is sensitive in detecting left coronary artery aneurysms. Generally, both coronary arteries are aneurysmally dilated in the proximal area. Most of the coronary artery lesions regress in size within a year while the rest have persistent aneurysm or narrowed, tortuous arteries or at least minor permanent damage.

The treatment of Kawasaki disease is supportive care. Until recently administration of high doses of aspirin was the treatment of choice, but this is now undergoing further study. It seems likely that a lower dosage of aspirin will be recommended in the near future. Steroid therapy is contraindicated. In an unpublished study of 300 patients by Drs Kusakawa and Yanagawa of Japan, patients treated with steroid therapy had a significantly higher incidence of aneurysm formation than children treated only with aspirin. Patients with cardiac abnormalities are observed closely during and following their initial illness and should be seen periodically throughout childhood and adolescence for further cardiac or vascular complications of the illness.

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Lyme Disease

LYME DISEASE is caused by a spirochete that can be found in blood, skin lesion or cerebrospinal fluid specimens. It has also been isolated from the nymphal and adult forms of its vector, *Ixodes dammini*. In California and Oregon, *Ixodes pacificus* ticks have been implicated. Cases have been widely distributed over the United States, Europe and the Far East.

Lyme disease typically begins in the summer with a unique skin lesion, erythema chronicum migrans, which usually lasts about three weeks, beginning as a red macule or papule that expands to form a large ring with central clearing. Annular lesions usually range from 6 to 52 cm in diameter; they may be absent or number more than 20 and last from three days to eight weeks. The rash may be accompanied by fever, headache, stiff neck, myalgias, arthralgias, malaise, fatigue or moderate lymphadenopathy. Weeks or months later, aseptic meningitis, meningoencephalitis, cranial neuropathies especially of the facial nerve, myelitis, migratory musculoskeletal pain, monoarticular or oligoarticular arthritis, myocarditis or atrioventricular node block may develop in certain patients. Radiculoneuritis may occur that is indistinguishable from brachial plexus neuritis. A Guillain-Barré-like syndrome, atypical in that it may show a cerebrospinal fluid pleocytosis in the range of 35 to 120 leukocytes, with 60% to 100% as mononuclear cells, has been described. Lymphocytic meningoradiculitis (Bannwarth's syndrome) has been associated serologically with Lyme disease. Serum cryoprecipitates, raised serum IgM levels and elevated erythrocyte sedimentation rates may occur.

Penicillin or tetracycline given for ten days can successfully treat the early phases of the disease when rash is present and can prevent, or at least ameliorate, the subsequent arthritic, neurologic or cardiac disorders.

Diagnosis can be confirmed by the finding of raised levels of IgG or IgM antibodies to the spirochete using indirect immunofluorescence, or by isolating the spirochete. These tests are presently of limited availability except through state departments of health, so local laboratory personnel should be alerted to the specific diagnostic concern when considering this disease.

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Pneumococcal Polysaccharide Immunization

IMMUNIZATION WITH pneumococcal polysaccharide vaccine is a safe and effective means of increasing a specific antibody and providing protection against overwhelming infection from *Streptococcus pneumoniae*. It is generally agreed, however, that immunization should be restricted to specific populations at high risk for infection.

Those patients who should be immunized include persons with increased susceptibility to infection but in whom a normal antibody response can develop following immunization. Specific diagnoses include sickle cell disease, splenectomy following trauma or for hematologic disorders, aging (that is, older than 55 years of age), complement disorders and nephrotic syndrome. Patients who might benefit from immunization but who have an impaired antibody response include those who have Hodgkin's disease with splenectomy, multiple myeloma and other malignant disorders. Many patients who are susceptible to overwhelming infection have severely impaired immunity and would not be expected to benefit from immunization. These include patients who have hypogammaglobulinemia and severe abnormalities of both T-cell and B-cell immunity. Patients with chronic lung disease who do not have an increased susceptibility to *S pneumoniae* infection, such as those who have asthma or cystic fibrosis, should not be immunized.

Immunization should be given to children 2 years

of age or older, as the antibody response to pneumococcal polysaccharide is significantly reduced in infants. However, selected patients who are at high risk for *S pneumoniae* infection or who have repeated infections may receive some benefit from immunization given at 9 months of age and followed by a booster at 2 years. In children older than 2 years of age and in adults, booster immunization should not be given before three to four years following primary immunization, as significant local and systemic reactions may occur. Recent evidence indicates that antibody levels to pneumococcal polysaccharide are reduced four years following primary immunization in older children and adults.

Several pneumococcal polysaccharide preparations are available for immunization. All contain 23 individual polysaccharides that have the ability to protect against 90% to 95% of *S pneumoniae* organisms that may cause infection. Immunization is given as a single subcutaneous dose of 0.5 ml. Local reactions, which are infrequent, consist of pain and swelling at the site of infection. Rarely, patients may experience more extensive swelling of the arm or systemic reactions such as fever, or both. Severe systemic reactions are extremely rare.

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α-Fetoprotein Screening

α-FETOPROTEIN is a serum protein that is normally found only in fetuses and is excreted via fetal urine into amniotic fluid. It probably reaches maternal serum via the placenta and possibly across the fetal membranes. Certain fetal abnormalities including surface defects allow fetal fluids containing high levels of α-fetoprotein to leak into amniotic fluid. Serum α-fetoprotein levels never exceed about 10 ng per ml in normal adults except in pregnancy.

Anencephaly, spina bifida and encephalocele, collectively called neural tube defects, are relatively common causes of fetal and infant death and survivors are often seriously handicapped. The incidence in the western United States is between 1 and 2 per 1,000 births. About 90% of infants with neural tube defects are born to couples who do not have a family history of this disorder and can be identified prenatally only by screening all pregnancies.

Several pilot studies confirm that at least 90% of cases of anencephaly and 80% of cases of open spina bifida can be identified prenatally by measuring α-fetoprotein levels in maternal serum. Laboratories involved in screening should have established their own normal α-fetoprotein range for each week of pregnancy from 15 through 22 weeks. Accurate gestational dates are essential, as serum α-fetoprotein levels increase by about 10% to 15% in each week over this period. Most protocols recommend a second blood test if the serum α-fetoprotein level exceeds the 95th percentile, followed by a sonogram if this is also elevated. In about half of these cases, a high serum α-fetoprotein level is explained by the presence of twins, incorrect gestational dates and, occasionally, fetal demise. Amniocentesis is recommended for the remainder of cases (about 1% to 2%) after a detailed ultrasound examination of the entire fetus. α-Fetoprotein assay of amniotic fluid should be combined with acetylcholinesterase gel electrophoresis, and repeated ultrasound examinations and biochemical testing may be necessary to confirm the diagnosis.

Maternal serum α-fetoprotein screening will identify a group of women at risk for an abnormal fetus. The ultimate diagnosis requires both sonography by experienced personnel and biochemical studies of amniotic fluid. The risk for a case of open neural tube defect after one elevated serum α-fetoprotein level is 1 in 50 and 1 in 15 at amniocentesis. The chance of terminating the pregnancy of a normal fetus is exceedingly small (less than 1 per 100,000) providing the protocol described is followed. Of women without fetal abnormalities, 80% can anticipate a normal pregnancy outcome, but there is about a fourfold increased risk of late pregnancy problems, such as fetal death and low birth weight. The early identification of twins and higher risk pregnancies are positive aspects, while anxiety generated by an abnormal serum value and an increased number of sonographies and amniocenteses are negative aspects of maternal screening.

It is anticipated that maternal serum α-fetoprotein screening will become a more generally available voluntary pregnancy test in the near future. This will require the coordination of laboratories and prenatal services, as well as educational programs and counseling services.

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Growth Hormone Therapy

FOR ALMOST three decades pituitary-derived human growth hormone has proved an effective treatment for children with absent or low growth hormone concentrations measured by radioimmunoassay of serum after stimuli by growth hormone secretagogues. Low plasma concentrations of somatomedins, growth hormone-dependent peptides believed to directly stimulate growth, are characteristic of such patients. Five years ago cases of short, poorly growing children with normal immunoreactive growth hormone and low somatomedin concentrations were described. Because they grew and their somatomedin levels rose when exogenous growth hormone was administered, they were considered to produce biologically inactive growth hormone that was still reactive in standard growth hormone radioimmunoas-

says. Last year the range of growth hormone-responsive patients was broadened when otherwise healthy but extremely short and poorly growing children with normal growth hormone values were treated with growth hormone regardless of somatomedin level; 6 of the 15 treated with conventional doses had improved growth rate of at least an additional 2 cm per year, and 4 of these had normal somatomedin values before therapy. These patients may have had severe forms of constitutional delay in growth or genetically short stature, but the possibility of a subtle disorder of growth hormone secretion has not been eliminated. Thus, growth hormone testing or measuring somatomedin values cannot always determine which child will respond to growth hormone therapy.

Previously, growth hormone was available in limited supplies from the National Pituitary Agency for carefully screened patients with classical growth hormone deficiency; presently, natural (and soon biosynthetic growth hormone) can be obtained from commercial sources and there may be less scrutiny of the selection of patients. This increased availability of growth hormone will allow more children to be treated, but the possibility of side effects and the high cost of therapy should temper the choice of recipient. At present, the only definitive indication for growth hormone therapy is proved growth hormone deficiency after provocative testing; the other types of growth hormone-responsive patients described above were extremely short (below the third percentile for age), growing very poorly (less than 4.5 cm of growth per year between 4 and 9 years of age) and otherwise free of disease, and all were treated in research protocols after informed consent was obtained. The use of growth hormone in children of greater height and better growth rate has not been established as safe or effective. It is clear that carefully controlled clinical trials using a larger number of children must be done before the range of patients that receive treatment is widened.

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Diagnosis and Management of Amebic Liver Abscess in Children

AMEBIASIS has a cosmopolitan distribution throughout the world and is found from pole to pole. Good prevalence data do not exist for the United States, but studies suggest that between 1% and 7% of the population is infected with *Entamoeba histolytica*. Less than 1% of those infected will have extraintestinal disease. Fulminant disease is most common in children younger than 4 years of age and infants may have a particularly rapidly progressive course. Mortality increases when there is a failure to recognize the disease, which may not be considered in the differential diagnosis.

The liver is the most common site of extraintestinal infection with *E histolytica*. Only a few patients will have intestinal disease at the time of presentation. Symptoms may be present for from a few days to a month. In children fever, anorexia, abdominal distention and abdominal pain, most often in the right upper quadrant, are the most common complaints. The pain is usually dull, but stabbing, pleuritic-like pain may be present. Cough and sweating are present in about 10% to 15% of patients. Abdominal distention and tenderness may be the only complaints in young infants. On physical examination the liver is usually found to be enlarged and having point tenderness to palpation. Localized swelling may occasionally be seen as well as a tympanitic and distended abdomen. Laboratory studies may show anemia and a leukocyte count of more than 10,000 per μl with a left shift. Eosinophilia is generally absent and liver enzyme levels are normal or only slightly raised. Serology for amebiasis is positive in 95% to 98% of cases. Indirect immunofluorescent antibody, counterimmunoelectrophoresis, indirect hemagglutination and immunodiffusion serodiagnostic tests are available at public health and private laboratories. Titers may not be positive very early in infection and in very young infants.

An upright x-ray film of the abdomen may show elevation of the right hemidiaphragm, segmental atelectasis of the lower lobe or effusion. Sonography is a noninvasive imaging tool that is useful in diagnosing and managing hepatic abscess in children. In most cases, the ultrasound findings for amebic hepatic abscess are not totally specific; however, Ralls and co-workers have described a constellation of findings that they consider to be a "suggestive sonographic pattern." This pattern consists of a lack of significant wall echoes; a round or oval configuration; echogenicity less than that of normal liver parenchyma with fine, homogeneous, low-level echoes at high gain; a location contiguous to the liver capsule, and distal sonic enhancement. If the sonogram findings are nondiagnostic and there is a strong suggestion of amebic liver abscess or a positive serology, a technetium Tc 99m liver scan should be done. The sonogram may be repeated during and after therapy to follow the clinical course of the patient.

The abscess cavity may be large or located subphrenically or in an area where rupture into the peritoneal cavity is possible. In these cases percutaneous aspiration of the abscess using a medium- or large-bore needle is suggested. Some investigators believe that aspiration of the abscess may reduce morbidity and mortality. The aspiration may be facilitated by ultrasonography, by which the area of the abscess cavity can be mapped. The cavity should be entered at the point of maximum tenderness.

Metronidazole, 35 to 50 mg per kg (maximum 750 mg), given orally each day in three divided doses for

ten days, is adequate to treat most cases. Metronidazole may be given intravenously to patients unable to tolerate oral medication. Nausea and abdominal upset are common side effects of this drug. Emetine hydrochloride, 1 mg per kg a day (maximum 60 mg) for five days, or dehydroemetine, 1.5 mg per kg a day (maximum 90 mg), both given with chloroquine phosphate, 10 mg per kg base per day for 21 days (maximum 600 mg a day), is an alternative therapy. Although cardiotoxicity is a common side effect of emetine in adults, it is not generally a problem in children. Because emetine and dehydroemetine must be given intramuscularly and are potentially toxic, treatment should be given in hospital.

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Prevention of Kernicterus

WITH THE USE of exchange transfusion to control the hyperbilirubinemia resulting from hemolytic disease in newborn infants, the clinical features associated with kernicterus largely disappeared 20 years ago. The classical neurologic findings of opisthotonus seen in the nursery and athetoid cerebral palsy seen in follow-up clinics no longer occur. The yellow staining of the brain at autopsy has not disappeared, however, but now occurs most often in small premature infants and frequently at low bilirubin levels. The yellow staining is associated with asphyxia, acidosis, hypothermia and other morbid conditions in these small infants. The concept of potentiating factors that increase the risk for kernicterus at low bilirubin levels was developed to explain these findings. Exchange transfusion at bilirubin levels of 10 to 15 mg per dl in the presence of "potentiating factors" was recommended as treatment for this problem and adopted without confirming clinical trials. In spite of careful adherence to this practice, the incidence of yellow staining of the brain at autopsy did not disappear, especially with longer survival of infants of low birth weight and gestation in the nursery.

In an effort to find clinical factors that would predict kernicterus and indicate when to start preventive treatment, clinical studies were reported in 1980 and 1982 from several neonatal services including our own. When the records of infants dying with kernicterus were compared with those of infants dying without kernicterus, no factors including peak bilirubin levels could be found that distinguish the former group. "Predisposing factors" predispose to death rather than kernicterus.

The significance of the yellow staining remains in question. In our cases the expected microscopic neuronal injury was lacking and spongy changes associated with anoxia were found instead. This suggests that bilirubin staining does not indicate bilirubin toxicity in these infants but rather reflects prior damage to the brain cells.

The mechanism by which bilirubin staining occurs is also not settled. The concept that only unbound bilirubin in plasma is free to enter the cells is being reexamined. In a recent paper by Levine and co-workers, staining was found irrespective of the bilirubin level when the blood-brain barrier was experimentally opened. Albumin-bound bilirubin was able to enter the brain cells under these circumstances. Many factors used in the treatment of high-risk newborns, including infusion of hypertonic solutions, will affect the blood-brain barrier. Exchange transfusion will not prevent bilirubin staining of the brain at low levels of bilirubin and, in view of the experimental work quoted above, may actually be harmful.

The concept of "potentiating factors" that increase the risk of kernicterus at low bilirubin levels has been discredited by all the recent studies. The practice of doing exchange transfusions at low levels of bilirubin in infants with potentiating factors to prevent kernicterus should be abandoned.

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Prevention of Hepatitis B in Infants Born to HBsAg-Carrier Mothers

NATIONAL RECOMMENDATIONS for the use of both hepatitis B immune globulin (HBIG) and hepatitis B virus (HBV) vaccine for the prevention of hepatitis B in newborns were issued by the Advisory Committee on Immunization Practices (ACIP) almost two years ago. However, awareness and routine implementation of these recommendations have not been uniform in all areas. Part of this variation is due to the fact that additional studies of this complex problem have either been recently completed or are in progress and the results of these studies will likely lead to modifications of the current interim national recommendations. In addition, several specific questions regarding routine or selective implementation of these recommendations have been raised. I will address these questions.

- *Do all pregnant women need to be screened for the HBsAg-carrier state?*

To be able to give appropriate immunoprophylactics in the delivery room to infants of mothers who are carriers of hepatitis B surface antigen (HBsAg), it is necessary to know *before* delivery that the mother is HBsAg-positive. Whether all pregnant women should

be routinely tested for HBsAg is currently debatable because only about 1 to 5 per 1,000 women in the general population may carry the antigen. However, all women who belong to groups with known high HBsAg-carrier rates—that is, 1% or higher—should be tested before delivery. These include but are not limited to women from geographic areas such as parts of Asia and Africa where hepatitis B is very prevalent and women in health care occupations that involve routine contact with human blood. Results of limited studies in California of Chinese women born in the United States indicate that relatively high HBsAg-carrier rates persist in this population group even after several generations.

- *Do infants of all HBsAg-carrier mothers require immunoprophylaxis?*

There is a consensus that infants born to HBsAg-carrier mothers who are also positive for hepatitis B e antigen (HBeAg) or who lack anti-HBe should be given HBIG and HBV vaccine to prevent the development of a chronic hepatitis B virus infection. Infants born to HBsAg-carrier mothers who have detectable anti-HBe are considered at the lowest risk for the development of hepatitis B virus infection that may result in chronic HBsAg carriage. Available data, however, from both Europe and the United States suggest that there is a risk of about 1 in 100 to 1 in several hundred for severe (occasionally fatal) hepatitis B virus infection for infants born to both Asian and non-Asian mothers in this "low risk group." Such a risk cannot be ignored. According to national recommendations, *all* infants born to HBsAg-positive mothers, regardless of their HBeAg or anti-HBe state, should receive immunoprophylaxis.

- *What combination and schedule of HBIG and HBV vaccine should be used?*

The results of recent studies in Taiwan and the US indicate that if 0.5 ml of HBIG is given at birth followed by starting the regimen of HBV vaccine within the first month of life, no additional doses of HBIG are needed. Such a regimen was found to be about 90% effective in preventing chronic hepatitis B virus infections in infants born to HBeAg-positive mothers. Additional studies are under way in Burma and China that use only HBV vaccine starting at birth. Preliminary results suggest that high efficacy may be obtained without administering HBIG.

Definitive national recommendations will not likely be formulated for another year or two. Until then, the most current interim recommendation is for 0.5 ml of HBIG to be given as soon as possible after an infant has stabilized and preferably within 12 hours after birth. The efficacy of HBIG in preventing or modifying hepatitis B virus infection falls off substantially after 48 hours and is considered of little benefit after a week. In addition to the single dose of HBIG, three 10-μg (0.5 ml) doses of HBV vaccine should be given. The first vaccine dose can be given at the same time as the HBIG dose or at least within the first week. The second and third vaccine doses should be given at 1 and 6 months of age.

- *Can HBV vaccine or HBIG transmit AIDS?*

There have been ample speculation and concern regarding the possibility that these immunobiologics might transmit whatever may be the etiologic agent of the acquired immune deficiency syndrome (AIDS). Detailed review, however, of all of the relevant data regarding this possibility by a federal interagency committee has led to the conclusion that there are no epidemiologic or microbiologic findings to suggest that the HBV vaccine carries any etiologic risk for AIDS. An expert scientific committee of the World Health Organization stated in late 1983 that there has been no evidence of risk attached to the use of HBIG produced in the United States.

The prevention or modification of hepatitis B virus infections in infants born to HBsAg-carrier mothers deserves the highest priority. If efforts to prevent or modify infection are not begun as soon as possible after birth, many of these infants are irrevocably doomed to a high risk of severe liver disease, as there is no present cure or treatment for the HBsAg-carrier state once it is established. Obstetricians, pediatricians and family practitioners must work hand-in-hand to see that possible HBsAg-carrier mothers are identified and that their newborns receive appropriate and timely immunoprophylaxis.

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Treatment of Gastroesophageal Reflux

GASTROESOPHAGEAL REFLUX may present in an otherwise healthy infant as frequent spitting of formula or may be accompanied by severe symptoms such as pulmonary aspiration, failure to thrive and esophagitis. Symptoms usually occur before 3 months of age and resolve in 60% of infants by 18 months.

An important advance in our understanding of gastroesophageal reflux was the demonstration of upper gastrointestinal tract motility abnormalities in infants with this disorder, a finding previously noted in adults with reflux esophagitis. These findings have included delayed gastric emptying, decreased amplitude of peristalsis in the distal esophagus and decreased peristalsis in the body of the esophagus. Identification of specific motility abnormalities in individual patients allows tailoring of therapy.

Mild gastroesophageal reflux, defined as persistent

spitting of formula beyond the age of 3 months with normal growth and without pulmonary complications, is treated with elevation of the crib by at least 30 degrees, prone positioning, the elimination of "acid" foods and thickening of feedings. This treatment may be initiated without doing diagnostic studies, unless there is a suggestion of esophageal or gastric outlet obstruction.

In infants with severe symptoms compatible with gastroesophageal reflux in whom symptomatic therapy is unsuccessful, or in children who are older than 18 months of age, further studies are indicated to confirm the presence of the disorder. A barium swallow is done to rule out obstructive lesions such as esophageal webs or achalasia. Spontaneous gastroesophageal reflux occurring above the level of the carina is significant and is generally confirmed by other tests. If the barium swallow study shows no abnormalities or if respiratory tract symptoms are present, the esophageal intraluminal pH is monitored to determine whether gastroesophageal reflux is present and if it is associated with the observed symptoms. A radionuclide gastroesophageal scan may be done to quantitate gastric emptying and detect aspiration. Endoscopy with esophageal biopsy is indicated in selected patients with symptoms of esophagitis. If two of the above tests for gastroesophageal reflux or esophagitis are positive, the disorder is likely to be present with greater than 90% reliability and pharmacologic therapy is instituted.

Bethanechol chloride, a cholinergic agonist, decreases postprandial reflux time, improves acid clearance and improves weight gain in infants who have gastroesophageal reflux. It increases peristaltic amplitude and lowers esophageal sphincter pressure but has little effect on gastric emptying. The dose used is 9 mg per sq m of body surface a day in three divided doses, given orally 20 minutes before feeding. Irritability, tremors, diarrhea and bronchospasm in susceptible patients who have asthma are potential side effects.

Metoclopramide hydrochloride, which acts through dopamine inhibition in the central nervous system and gastrointestinal tract, is also used. Limited data in children suggest that gastroesophageal reflux-associated symptoms abate because of the drug's effect on gastric emptying. The dose is 0.1 mg per kg of body weight given before meals. Metoclopramide has central nervous system side effects such as rigidity and oculogyric crisis and is not recommended for infants younger than 6 months of age.

Domperidone, a peripheral dopamine antagonist currently under investigation, has gastrointestinal actions similar to metoclopramide but does not cross the blood-brain barrier. It may be useful as it has less nervous system toxicity. Antacids are indicated if gastroesophageal reflux persists or if symptoms of esophagitis are present. Cimetidine, a histamine H_2-receptor antagonist, may be added, though there have been no controlled studies of its value in infants.

Patients who do not respond within six to eight weeks of intensive medical management or who have severe complications such as apnea or esophageal stricture should undergo an antireflux surgical procedure. The Nissen fundoplication consists of wrapping the fundus of the stomach about the distal esophagus and prevents gastroesophageal reflux while allowing normal esophageal emptying into the stomach. About 95% of infants with normal neurologic function will respond successfully to such a procedure and in infants with neurologic disorders about 60% will benefit. Short-term complications include the gas-bloat syndrome, manifested by the inability to burp or vomit. In long-term follow-up, about a third eat slowly (suggesting persistent esophageal dysmotility), but reflux remains well controlled.

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Doppler Echocardiography and Evaluation of Congenital Heart Disease

RECENT ADVANCES in ultrasound instrumentation have provided a combination of high-resolution two-dimensional echocardiographic imaging with the capability to identify the difference in frequency between the sound energy sent out and the sound energy backscattered from moving erythrocytes within a specifically localized area. This difference in frequency, commonly called the Doppler shift, is proportional to the velocity of the erythrocytes within the vessel or cardiac chamber. The technique, therefore, allows quantitative localized sampling of the areas of the heart and the calculation of instantaneous blood flow velocity within those areas, providing noninvasive evaluation of cardiac physiology in patients who have congenital heart disease. Some of these methods may obviate the need for cardiac catheterizations. Two areas of possible application of quantitative Doppler echocardiography include calculation of volume flow within cardiac chambers and vessels and noninvasive estimation of the gradients across stenotic cardiac valves.

Once blood flow velocity has been determined by an ultrasound Doppler system, the mean flow velocity and the cross-sectional area of flow can be used to calculate the volume of flow. Most applications of the Doppler method of calculating volume flow have been more accurate in children than in adults because the quality of the ultrasound images for measuring the flow area is better in children than in adults. Flows calculated from two areas—for instance, from the pulmonary artery and from the aorta—may be combined to calculate pulmonary-to-systemic flow ratio. In general, our experience with children suggests that comparing the pulmonary-to-systemic flow ratio by Doppler for simple atrial and ventricular shunts with the same flow ratio measured at catheterization yields a correlation coefficient of about 0.9 with a standard error of the estimate of about 0.35 to 1. These noninvasive flow

calculations can be used to differentiate patients with large, clinically significant left-to-right shunts from those with insignificant ones. We have found these techniques, while time-consuming, to be helpful in the serial management of patients.

The second Doppler method involves the prediction of transvalve gradients. The method is based on the Bernoulli principle in which the potential energy lost as blood goes from a high pressure area to a low pressure one across an obstruction is changed into kinetic energy. The velocity of erythrocytes is substantially higher downstream from the obstruction than it is proximal to the stenotic area. In a case of aortic stenosis, high velocity flow is detected and sampled in the ascending aorta. In pulmonary stenosis, high velocity occurs in the main pulmonary artery and is sampled under two-dimensional echo guidance. We and other investigators have found that this technique is simple to apply and yields gradient estimations with an accuracy of within 5% of measurements obtained at cardiac catheterization in cases of both aortic and pulmonary valve stenosis. Certainly, in pulmonary stenosis the method obviates the need for cardiac catheterization before submitting patients to a surgical procedure. In a case of simple aortic stenosis with normal ventricular function, cardiac catheterization can also be avoided. The gradient method has proved to be of substantial importance for serial study of patients as they grow because aortic stenosis of childhood is often a progressive disease.

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Monitoring for the Sudden Infant Death Syndrome

THE SUDDEN INFANT DEATH SYNDROME is a sudden and unexplained death, usually occurring between 1 month and 1 year of life. Sudden infant death syndrome accounts for about 2 deaths per 1,000 live births in the United States and represents the leading cause of infant mortality after the neonatal period. If there is enough evidence to explain the death, "sudden infant death due to _____" should be designated, which is distinct from the sudden infant death syndrome. The risk for sudden infant death is increased in neonatal survivors who were born prematurely and in infants born to opiate-addicted mothers. Compared with the overall incidence of about 0.2%, the risk for sudden infant death syndrome has been reported to be from 0.56% to 2% in subsequent siblings and 4% in a surviving twin.

Infants presumed to be "healthy" who have a "life-threatening event" may have received vigorous stimulation, mouth-to-mouth breathing or cardiopulmonary resuscitation from the parents or a babysitter. Some have referred to these infants as "near miss" for the sudden infant death syndrome when there is no specific diagnosis, but the more preferred term may be "apnea of infancy."

Knowledge regarding the cause and optimal management of prolonged apnea (cessation of breathing for 20 seconds or longer or a shorter respiratory pause associated with bradycardia, cyanosis or pallor) and its relationship to the sudden infant death syndrome is still limited. Most infants who have apnea of infancy survive, although the risk of sudden infant death occurring in this group is somewhat greater than in the general population. Many infants who have prolonged apnea are perceived by parents and physicians as having had a life-threatening event that may recur. The medical evaluation of these infants includes a careful history, physical examination, electronic cardiorespiratory monitoring and other appropriate studies done in hospital to determine the cause and severity. Apnea may be associated with such conditions as infections, metabolic aberrations, seizure, cardiac arrhythmias or congenital heart disease, airway obstruction, gastroesophageal reflux and impaired regulation of breathing.

In most cases, the pediatric evaluation and cardiorespiratory electronic monitoring can be initiated by a community pediatrician if these resources are available in a community hospital. In general, initial studies that may be helpful include a complete blood and differential count, arterial blood gas determination and chest radiograph. An electrocardiogram may be helpful if there are clinical findings suggesting arrhythmia, heart disease or pulmonary hypertension. If the history suggests seizure as a possibility, an electroencephalogram may be helpful. Other studies may be suggested by the clinical presentation and examinations. Appropriate treatment for a specific cause will often resolve the apnea problem.

When there is no diagnosis and the infant is asymptomatic, the risk for a recurrent episode of life-threatening prolonged apnea is unknown and home impedance apnea-cardiac monitoring may be used to detect prolonged apnea and alert the family to a possible "life-threatening episode." There is currently no single test or group of tests available to determine risk of prolonged apnea or the sudden infant death syndrome in an individual infant. Clinical follow-up should be arranged with the private medical doctor. Parents should keep records of monitor alarms, observations of the infant during an alarm and the type of intervention used. Consultation with a tertiary center is recommended if an infant continues to have unexplained prolonged apnea in hospital or if an infant, after discharge home, has recurrent apnea that requires vigorous stimulation or

resuscitation. About 40% of infants with apnea of infancy will not have a recurrence.

Management of asymptomatic infants who may be considered epidemiologically at increased risk for the sudden infant death syndrome is controversial. Home monitoring of other asymptomatic infants is not recommended as there are no reliable tests that predict an infant at risk for prolonged apnea or sudden infant death.

Home apnea-cardiac monitors and the alarm limits must be prescribed by an attending physician and should be continued until judged no longer appropriate. Most centers recommend impedance-type apnea-cardiac monitors with alarm limits for apnea and bradycardia. Parents and others involved in an infant's care must be taught monitor use and also cardiopulmonary resuscitation. Social support that includes trained relief personnel and 24-hour equipment service should be available.

Home monitoring may be discontinued when (1) an infant has had no "life-threatening" events for at least three months, or for two months if there have been no problems since the presenting episode; (2) the infant has not experienced a real monitor alarm for at least two months (at an apnea setting of 20 seconds and heart rate setting of 60 beats per minute); (3) during the asymptomatic period the infant must have had an upper respiratory tract infection, an immunization or another illness without recurrence of symptoms; (4) clinical evaluations that include neurologic, developmental and physical examinations show that the problems or initial reasons for monitoring have resolved, and (5) the infant has shown no abnormalities on cardiorespiratory recordings if those were present at the time of the infant's initial evaluation.

The etiology and optimal management of apnea of infancy is not clear and the actual relationship between apnea and the sudden infant death syndrome has not been established. Continued research in these areas is essential.

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Management of Congenital Hypothyroidism

In 1980 California began a newborn screening program for cases of congenital hypothyroidism. On filter-paper blood specimens, the serum thyroxine (T_4) level is measured followed by confirmatory thyroid-stimulating hormone (thyrotropin) levels on those samples with low T_4 values. The incidence of congenital hypothyroidism is about 1 per 3,750 live births and is confirmed by low T_4 and raised thyrotropin levels.

In October 1983 the California Newborn Screening Program began reporting as abnormal only those blood values that are presumptively positive for primary hypothyroidism—that is, blood specimens that showed low T_4 and raised thyrotropin values, indicating malfunction of the thyroid gland. Although relatively uncommon, other abnormalities such as low T_4 and low thyrotropin levels will be reported as normal for primary hypothyroidism. The most common disorders in which low T_4 and low thyrotropin levels occur include transient hypothyroxinemia, thyroxine-binding globulin deficiency and cases of premature infants and other sick newborns who have sick euthyroid syndrome. Thyroid disorders other than primary hypothyroidism, which include pituitary thyrotropin deficiency (secondary hypothyroidism) or hypothalamic thyrotropin-releasing hormone deficiency (tertiary hypothyroidism) and compensated hypothyroidism (normal T_4 and raised thyrotropin levels), are also now reported as normal for primary hypothyroidism. A diagnosis of primary congenital hypothyroidism should be confirmed by repeating serum T_4 and thyrotropin determinations in a local laboratory. The primary physician must not rely on the state's screening program when there may be a thyroid disorder other than primary hypothyroidism. Thyroid function tests should be done in a local laboratory whenever clinically indicated.

Once a primary physician has been notified that primary hypothyroidism may be present, confirmatory T_4, triiodothyronine resin uptake and thyrotropin levels should be determined in a local laboratory. A thyroid scan using either sodium pertechnetate Tc 99m or sodium iodide I 123 is helpful in determining abnormal development of the thyroid gland. An x-ray film of the knee and ankle for skeletal maturation often shows delayed development and is helpful in determining the duration of hypothyroidism.

Therapy for congenital hypothyroidism should consist of levothyroxine sodium (Synthroid), 8 to 10 μg per kg of body weight a day. With advancing age the dose of levothyroxine decreases to 4 to 6 μg per kg a day in 1- to 5-year-old children and 3 to 4 μg per kg a day in adolescents. Dosages of levothyroxine must be individualized to keep serum T_4 levels in the normal range for age. T_4 levels normally peak at 1 to 3 days of age and reach values of 12 to 22 μg per dl. T_4 levels in preterm infants are lower than those in term infants. After 2 weeks of age and throughout infancy and early childhood, the T_4 levels are about 7 to 15 μg per dl. The T_4 level then gradually decreases to 4.5 to 12.5 μg per dl after 15 years of age, when the normal adult levels are reached.

With inadequate thyroid hormone replacement, growth and mental development may be impaired, even though other signs and symptoms of hypothyroidism are absent. With overtreatment craniosynostosis can occur and, in addition, animal studies suggest a toxic effect on brain development. Maintenance of T_4 levels in the upper half of the normal range for age is recommended.

Initially, raised thyrotropin levels decrease with appropriate thyroid hormone replacement but may take

several weeks or months before returning to normal. T_4 values that are borderline or in the low-normal range for age with raised thyrotropin values indicate inadequate hormone replacement and the dose of thyroid hormone should be adjusted accordingly.

It is well known that untreated congenital hypothyroidism is associated with mental retardation. The prognosis for mental function, however, is substantially improved with treatment in early infancy. Although with early treatment intelligence is often normal, recent studies indicate some impairment of brain function by 18 months of age. The most important factors affecting mental development appear to be the duration and severity of hypothyroidism in a fetus. Early diagnosis and appropriate treatment are the only measures available to minimize these effects on mental development.

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Editorials

The Psychobiology of War

ELSEWHERE IN THIS ISSUE is a commentary on health belief systems and the psychobiology of war by Neil J. Elgee, who is a respected internist in the Pacific Northwest. Dr Elgee has attempted what many physicians would like to see done—that is, to find a biologic or health science approach to dealing with the threat of nuclear war that would go beyond dire warnings from the medical profession of the "stupendous devastation of a nuclear war and the helplessness of the medical community to heal anything thereafter." He has obviously given this a great deal of thought and devoted much time to its study. His commentary is worth the attention of any physician who is concerned about this problem, and that should be all of us. MSMW

The Vertiginous Patient—When to Get a CT Scan of the Brain

THE VESTIBULOCEREBELLUM has been called the "fifth vestibular nucleus" because it receives primary vestibular afferents and is highly interconnected with the brainstem vestibular nuclei.[1] Lesions involving this part of the cerebellum produce vertigo, nystagmus and gait instability—symptoms that can also be produced by more benign peripheral vestibular lesions. As Dr John Hotson points out in this issue of the journal, it is important to recognize early infarction or hemorrhage involving the vestibulocerebellum because associated swelling may lead to compression of the brain stem, coma and respiratory arrest. Surgical decompression can be lifesaving.

Fortunately, most lesions involving the vestibulocerebellum also involve the lateral cerebellar hemispheres or the brain stem (or both) so that multiple associated symptoms and signs make the diagnosis of a central lesion obvious. Occasionally, however, hemorrhage or infarction is confined to the caudal midline cerebellum, and vestibular symptoms and signs predominate. As Dr Hotson notes, it is clearly inappropriate "to treat every vertiginous patient as if they have a potentially fatal stroke." It is equally inappropriate to do computed tomographic (CT) scanning of the brain on every vertiginous patient. Dr Hotson, therefore, outlines practical clinical means for separating acute benign labyrinthine disorders from strokes involving the vestibulocerebellum.

With regard to the history, I have not found a patient's description of vertigo to be particularly useful for separating central from peripheral causes. Patients typically have difficulty in deciding if they are rotating or whether the environment is rotating and in which direction the rotation is occurring. This confusion probably results from conflicting signals arriving via the vestibular, somatosensory and visual pathways, making it difficult for a patient to decide which signals to believe.

Of the clinical signs that distinguish acute benign labyrinthine disorders from lesions involving the vestibulocerebellum, I have found the nature of the nystagmus and gait instability most useful. Peripheral vestibular lesions result in unidirectional spontaneous nystagmus that is inhibited with fixation, while lesions of the cerebellum typically result in direction-changing gaze-evoked nystagmus that is poorly inhibited with fixation.[2(pp108-118)] The gait instability associated with acute lesions of the vestibulocerebellum is usually profound and patients are unable to stand without assistance. By contrast, although patients with acute peripheral vestibular lesions fall toward the side of the lesion, they can stand and walk with minimal assistance. If not clear initially, the course within the first 48 hours should distinguish between a benign peripheral and a more worrisome central disorder. The central nervous system has a remarkable ability to compensate for peripheral vestibular loss in part through activity of the vestibulocerebellum. The spontaneous nystagmus and the gait imbalance with acute peripheral vestibular lesions rapidly diminish within the first 48 hours. Lack of rapid improvement or deterioration should raise concern for a possible central lesion.

Electronystagmography (ENG) can also be useful for separating peripheral from central causes of vertigo.[2(pp125-128)] By recording spontaneous nystagmus with eyes opened in darkness or with eyes closed, the effect of fixation can be accurately assessed. Lack of suppression or an increase with fixation suggests a central lesion. Unilateral caloric hypoexcitability suggests a peripheral vestibular lesion while symmetrical hyperactive caloric responses occur with lesions of the vestibulocerebellum. Because the vestibulocerebellum is a critical center for visual-vestibular interaction, lesions involving this structure severely impair a patient's ability to modify vestibular responses with vision. Visual-vestibular interaction can be quantified with ENG by having the patient fixate on a target during the caloric test or while being rotated about the vertical axis. In normal persons or in patients with peripheral vestibular lesions the slow-phase velocity of vestibular-induced nystagmus decreases by more than 50% with fixation. By contrast, there is little change in nystagmus slow-phase velocity with fixation in patients with lesions of the vestibulocerebellum.

Which vertiginous patients require a CT scan of the brain? Dr Hotson suggests that an elderly patient or one at risk for stroke in whom findings deviate from the expected findings of a unilateral peripheral vestibular lesion requires prompt evaluation for a cerebellar in-

farction or hemorrhage. This is a reasonable formula that places proper emphasis on the clinical assessment. By way of review, the expected findings with an acute peripheral vestibular lesion are mild to moderate gait instability with a tendency to fall toward the side of the lesion, unidirectional spontaneous nystagmus that is inhibited with fixation and rapid improvement within the first 48 hours. Clearly, a small minority of vertiginous patients require a CT scan of the brain to rule out a cerebellar hemorrhage or infarction.

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Hyperinfection Syndrome in a Renal Transplant Recipient

ELSEWHERE in this issue Dr Hirschmann and co-workers discuss in detail a case of strongyloidiasis in a patient who had had a renal transplant. It is seldom that we find such an abundance of medical wit and philosophy dispensed in equal measure with diagnostic acumen in a clinicopathologic conference. In addition to reaching a correct diagnosis, the discussant covered very well virtually all of the important clinical aspects of strongyloidiasis.

Before expanding a bit on some features of strongyloidiasis, it might be appropriate to at least mention another parasite, namely *Toxoplasma gondii,* that might have been considered in association with such complicated illness in an immunodeficient host. While toxoplasmosis can cause skin lesions and pulmonary involvement, the skin lesions are likely to be vasculitic and definitely not pyogenic in nature. The pulmonary lesions are also much less prominent and nondescript in nature. In addition, central nervous system invasion is often a terminal feature of toxoplasmosis in an immunocompromised patient.

Bringing the discussion back to strongyloidiasis, one of the first points to emphasize is that exposure to this parasite does not require travel to or residence in the tropics. While strongyloidiasis is much more common in certain geographic areas, such as in Southeast Asia, it also occurs in the United States. In fact, the parasite is better adapted to transmission in an unsanitary environment than many other intestinal helminths by virtue of its rapid transformation to the infective stage. This may help explain why infection with *Strongyloides stercoralis* is seen in mental institutions and in asylums where hygienic conditions are more often compromised.[1]

Incidentally, the Australian experience referred to by Dr Hirschmann in World War II soldiers interred in Japanese prisoner of war camps was also reported from England.[2] A similar experience has been noted also in the United States military during World War II by Pelletier.[3] This documentation indicates that parasites from some areas of the world are capable of persisting indefinitely in a human host, presumably by a low level of internal autoinfection, and this raises an interesting question as to why immunity in this infection is not more effective.

The pulmonary symptoms present in the case described in this issue deserve a few additional comments. First, the adult female parasite may sometimes be found in the lungs as well as in the upper small bowel, so that larvae found in sputum may be produced there and not be simply in transit through the lungs. In fact, in this particular case the larvae shown in Figure 2 of the Specialty Conference in this issue are compatible with larvae transiting the lungs, at or beyond the filariform stage, rather than the rhabditiform stage. If authentic rhabditiform larvae are seen in the sputum this is an indication that female worms are present and the infection may be somewhat more difficult to treat than if the infection is only intestinal.

Another point with regard to pulmonary involvement is that in some patients asthmatic symptoms develop with *Strongyloides* infection. The wheezing and dyspnea described in this patient may have been due to bronchial constriction on an allergic basis and not simply to a Gram-negative pneumonia. Occasionally, the prominent asthmatic features of *Strongyloides* infections seen in some patients may be reminiscent of tropical pulmonary eosinophilia with diffuse pulmonary infiltrates bilaterally, leukocytosis and a striking degree of eosinophilia. Incidentally, eosinophilia is very commonly seen in patients infected with *S stercoralis,* although usually a patient has an eosinophilia on the order of 10% to 25%. In this case, of course, eosinophilia may have been suppressed by the large doses of steroids or, as pointed out by Dr Hirschmann, some patients with overwhelming strongyloidiasis, even when not receiving steroids, do not mount a peripheral eosinophil response. A recently described enzyme-linked immunosorbent assay test for antibody to larval antigen may be helpful in diagnosis because larval excretion can be irregular and laboratory personnel may be inexperienced in examining stool or sputum specimens for larvae.[4]

It is interesting that diffuse pulmonary infiltrates are frequently described in fatal cases of strongyloidiasis reported in the literature. The pathologic description in these cases often comments on the hemorrhagic lungs. This is of some interest because in recent work with a monkey model of overwhelming strongyloidiasis it was reported that hemorrhagic lungs are an invariable feature of fatal overwhelming *Strongyloides* infection in the patas monkey.[5]

Finally, I would take exception with one of the points made in the discussion of the case that the finding of filariform larvae in a stool or sputum specimen makes a diagnosis of overwhelming strongyloidiasis conclusive. Certainly the finding of filariform larvae in a sputum specimen indicates that larvae are transiting

the lungs and that some degree of internal autoinfection is taking place. However, depending on conditions of gastrointestinal motility and the speed with which fecal material transits the bowel, and the newer appreciation of the fact that perhaps most infections with this parasite involve some degree of internal autoinfection, the interpretation of filariform larvae in the stool must be more guarded. The term "overwhelming strongyloidiasis" has been used in the literature synonymously with hyperinfection syndrome, both somewhat ambiguous expressions. I prefer the term hyperinfection syndrome to indicate a clinical situation in which there is widespread larval invasion of many tissues and a severe degree of internal autoinfection.[6] Perhaps the term hyperinfection should carry a certain connotation of the clinical state of a patient as well, because it should indicate a *Strongyloides* infection that is out of control both clinically and parasitologically.

Fortunately, there was a happy ending in this case because the diagnosis was made in time to initiate specific therapy and thus the infection was controlled and the patient recovered. In view of the many reports in the literature on hyperinfection syndrome, it is apparent that the ending is not always such a happy one.

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Where Should the Hard Decisions in Health Care Be Made?

ONE SENSES THAT there is a slow but perceptibly growing awareness that there will be hard decisions ahead in health care. Just what these decisions will be remains murky in the minds of many of us. At the same time it is becoming very clear that things cannot go on as they are indefinitely. Rising expectations and rising costs are on a collision course with relatively limited resources that can never be sufficient to meet all the demands and expectations for health care. It seems that the hard decisions to be made will boil down to who will get what kind of health care, and the question is where should these decisions be made?

Very briefly, the root causes of the rising costs are the new science and new technology being applied in patient care, the fact that someone other than the patient or provider pays most or all of the costs and that the population as a whole is aging rapidly and requiring more and increasingly expensive care. None of this is easily changed in our society. In fact, there will be more science and technology, more elderly people and higher health care costs for the foreseeable future. The efforts at cost containment have proved no match for these causes of rising costs, nor are they likely to. The list of cost containment measures is familiar. They have been little more than generally very expensive Band-Aids. Stronger measures may well be imposed by those who pay the costs, whether in the public or private sector, but these will be difficult to enforce. Any efforts to limit care will be resisted by patients and providers alike, because Americans have been educated to know what good care is and to expect it. And the courts are likely to support a patient's right to care of good quality, and indeed they are already doing this without any particular regard for the impact of their actions on cost. All of this is to say that the outlook for cost control in patient care by any of the means that have been tried to date seems bleak indeed. On the contrary, further increases in health care costs appear inevitable.

But if rising health care costs are an irresistible force, by the same token, the limits on what can be afforded for health care will eventually become a relatively immovable object. As this occurs the hard decisions will have to be faced when it becomes evident that everything cannot be done for everybody. What are some of the options? One might be to say that you can have it if you can pay for it; otherwise, tough luck. Another might be simply to restrict what is available to what can be afforded for everyone. Neither of these options would seem to be acceptable to the American people, although some compromise between them might be. But any compromise will pose difficult social, ethical, economic and political problems in our interdependent yet independent, very human and very technologic society. Some of these are already becoming all too obvious as some of the hard decisions begin to be faced.

Already in the "Baby Doe" controversy a fundamental question has been raised. Should these hard decisions (in this case whether substantial resources, both human and technologic, will be used to save a very severely compromised infant) be made by applying a federal law, or should they be made by some kind of a consensus reached among those most directly involved? In this controversial case the federal government seems bent on playing the role of "Big Brother" who knows best, while the courts, the health professionals and a very distressed family believe this kind of hard decision is better made in individual situations by those in a position to know more precisely what is at stake for all concerned. This issue and all the hard questions about who will get what kind of health care are issues that strike at the heart of what America is all about.

It is tempting to turn to government, to say that this is what governments are for—to solve problems like this in the best interests of all the people. But there is something different about health care. It is something very personal and it often pits one person's individual

interest against what may be the collective interest of all the people. Governments can act only through legislation, regulation, administrative enforcement and the courts. In our system legislation often responds to special interest groups, regulations provide mechanical formulas to decide who gets what, cost containment is being practiced by systematic underfunding (which results in some form of rationing of health care) and the courts try to settle the conflicts that inevitably arise in their own lumbering and sometimes bumbling fashion. None of this is very sensitive to the hard questions in health care, nor does it seem likely to work well, if at all.

We return to the thought that these hard decisions may best be made by agreement or consensus among those most directly involved. This has an additional advantage in that those who have reached agreement on what is to be done are then likely to support rather than resist the decision. The principle can be extrapolated from an individual hard decision in patient care to hard decisions in health care that might be made at a community, regional or even national level. In this way sensitivity to personal, community, regional and national needs can be considered in relation to the available resources, and the hard decisions in health care made by those likely to have to carry out the decisions. As one thinks about it, this seems almost the only humane or rational way to reach sensitive decisions of this nature.

Is there any reason for optimism? Perhaps there is some. Almost everyone involved in health care is developing greater sophistication about costs. There is more discussion of ethical problems in health care by many of those most concerned. For some years there has been a trend toward decentralization of authority and power in health care. And there is evidence of increasing involvement of all who should be involved at community, state and national levels. The stage is being set. But there is much public and professional education to be done if the problems are to be recognized for what this writer believes they are. It would be tragic if the present trends toward discussion and decentralization were to become reversed, and in some kind of desperation over rising costs, the nation were to turn to the federal government to control these costs no matter what the consequences to health care. This is conceivable. But it would be a sad confession that our democratic system could not find ways to adapt its very democracy to meet changing needs in our increasingly complex and interdependent human and technologic society.

MSMW

Case Reports

Q Fever Endocarditis

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ENDOCARDITIS is a rare and often fatal complication of Q fever.[1] Fewer than 100 cases have been reported worldwide and only five from the United States.[1-4] The increasing prevalence of *Coxiella burnetii* in dairy cattle in some areas of the United States[1] may yet result in the more frequent occurrence of Q fever in humans.

Endocarditis due to *C burnetii* develops during chronic multisystem infection (chronic Q fever). Each of the 16 patients in a recent report[5] had chronic liver as well as other organ involvement before development of endocarditis. There is some speculation that active hepatic infection may be the source of chronic exposure of the heart valves to *Rickettsia* sps.[1,5]

We present two cases of endocarditis complicating chronic Q fever that exemplify the difficulties in diagnosis and management presented by this occurrence.

Reports of Cases

CASE 1. The patient, a 74-year-old woman, received a porcine mitral valve heterograft for rheumatic heart disease in March of 1974 following a long-standing history of mitral stenosis and pulmonary hypertension. She was well until March of 1976, when fever, chills, dyspnea, tachycardia and diaphoresis developed. She was admitted to hospital at that time and treated for acute pulmonary edema. Tetracycline was given as empiric treatment for a urinary tract infection. About two weeks after discharge from hospital she had another episode of acute pulmonary edema and fever to 39°C (102°F) and was readmitted to hospital. The diagnosis of endocarditis was considered. Cultures of blood specimens taken at five different times and of urine and sputum specimens were reported as negative. Empiric treatment with tetracycline resulted in resolution of the fever within 24 hours. Echocardiogram failed to show valvular dysfunction. Her fever recurred after discharge and she was treated with prednisone from May to December of 1976 without effect on her fever. An intravenous pyelogram in September of 1976 showed no abnormalities. In March of 1977 she was admitted to hospital with confusion and generalized weakness, fever and orthopnea. Blood cultures were again negative.

In April of 1977 she was transferred to the Stanford University Medical Center for evaluation of her central nervous system signs and suspected culture-negative endocarditis. At that time there were daily fevers of 38°C to 39°C and microscopic hematuria. The erythrocyte sedimentation rate was 101 mm an hour and protein was noted in the urine. A latex-fixation titer for rheumatoid factor was 1:2,560 with a negative antinuclear antibody titer and a nonspecific increase in γ-globulin fraction on serum protein electrophoresis. A long-standing mitral regurgitant murmur was heard and a new, low-grade aortic murmur was detected and confirmed by echocardiogram. A sector scan showed a probable bicuspid aortic valve without regurgitation. Cultures of many blood specimens obtained over a three-week period (including specimens taken at cardiac catheterization, arterial blood and blood inoculated in hypertonic media) failed to show the cause of what was clinically diagnosed as endocarditis of the aortic valve. Treatment with vancomycin hydrochloride and gentamicin was begun on May 14, 1977, and her temperature returned to normal. When gentamicin was discontinued after one week because of renal toxicity and vancomycin continued, her fever returned to 38°C.

At this time, a *C burnetii* phase II titer of greater than 1:2,048 was reported by the California Health Department, and the diagnosis of Q fever endocarditis was considered likely. Doxycycline and tetracycline were each given for several days but had to be discontinued because a rash developed. The combination trimethoprim (160 mg) and sulfamethoxazole (800 mg) was then given twice a day. Her temperature remained normal thereafter and her aortic murmur gradually disappeared. The anemia, elevated erythrocyte sedimentation rate, slightly raised liver function values and microscopic hematuria all resolved over a period of several weeks. A phase I *C burnetii* titer of 1:2,048 confirmed the diagnosis of chronic Q fever with endocarditis. The phase I titer gradually declined to 1:512 and finally to 1:256 after 27 months of continuous administration of the combination of trimethoprim and sulfamethoxazole. During this time, no signs or symptoms of recurrent endocarditis were noted.*

CASE 2. A 56-year-old man, a construction worker, underwent aortic valve replacement for rheumatic heart disease in 1969. In July of 1977 he had an upper respiratory tract infection with fever and nonproductive cough. Symptoms persisted despite empiric treatment with antibiotics. Daily fevers, night sweats and malaise

(Gallagher JG, Remington JS: Q fever endocarditis. West J Med 1984 Jun; 140:943-945)

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*Outpatient treatment was carried out by Martin Robinson, MD.

developed and a new aortic diastolic murmur was heard in September of 1977. During hospital evaluation at that time, anemia and abnormal liver function were noted. Cultures of several blood specimens were negative. A liver biopsy specimen showed granulomatous hepatitis without acid-fast bacilli. A bone marrow biopsy specimen showed only erythroid hyperplasia. A short course of tetracycline failed to modify signs or symptoms. Because of a positive tuberculin skin test and a history of recent exposure to active tuberculosis but with a series of negative sputum cultures, treatment with isoniazid and rifampin was started and he was discharged on a regimen of isoniazid and ethambutol hydrochloride. When six weeks of treatment failed to modify the fever, sweats and malaise, he was referred to the Veterans Administration Hospital in Palo Alto, California. Cultures of multiple specimens of blood, sputum, urine, cerebrospinal fluid and bone marrow were negative for bacteria, fungi, enteroviruses or mycobacteria.

The diagnosis of Q fever endocarditis was established at this time, based on a phase I *C burnetii* titer of 1:1,024. A regimen of tetracycline, 500 mg four times a day, and trimethoprim/sulfamethoxazole, eight single-strength tablets per day, was begun and the malaise, fever and sweats gradually resolved. The cardiac murmur persisted during nine months of outpatient follow-up. The phase I titers dropped substantially—1:1,024 in March of 1978 and 1:256 in May of 1978.

In August of 1978 he was readmitted with signs of heart failure. Cardiac catheterization showed severe regurgitation around the prosthetic aortic valve annulus. The phase I Q fever titer remained at 1:256. At operation to replace the prosthetic aortic valve, the process that led to failure seemed quiescent with much local fibrosis. Frozen tissue from the valve annulus was sent to the Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases, where guinea-pig and egg inoculation failed to isolate *C burnetti*. Additional cultures for bacteria, fungi and mycobacteria were done, as well as multiple blood cultures, none of which yielded any growth. Following successful replacement of the prosthetic aortic valve, he was discharged on a regimen of tetracycline every day and lincomycin hydrochloride monohydrate. After he had been asymptomatic with stable phase I titers (1:256) and normal liver function for several months, lincomycin therapy was discontinued in March of 1979. Tetracycline was discontinued a month later and he remained clinically stable off all treatment.*

Liver tissue obtained at the time of the acute infection was examined by fluorescence microscopy at the Rocky Mountain Laboratory. Foci of intracellular fluorescing particles were seen in the granulomas that were typical of *C burnetii* in staining properties.

Methods

Complement-fixation tests for antibodies against *C burnetii* phase I and phase II antigens were done either at the California State Department of Health in Berkeley (case 1) or at the Rocky Mountain Laboratory. Isolation attempts on the valve tissue and direct immunofluorescence on liver tissue from case 2, according to methods previously described, were done through the courtesy of Dr Richard Ormsbee of the Rocky Mountain Laboratory.[4]

Discussion

Q fever endocarditis is a rare complication of an uncommon disease. The illness evolves slowly as a multisystem chronic infection with *C burnetii*. Months or years usually elapse from the time of initial infection to the appearance of symptoms and the ultimate diagnosis of endocarditis.[1,5] Therefore, we were surprised to see two cases in one year. In each, the diagnosis of Q fever endocarditis was not suspected initially. Various periods of time elapsed and a number of empiric therapies were tried without effect.

Abnormal heart valves with preexisting damage are most often affected, and a case of prosthetic valve endocarditis with Q fever has also been reported.[5] Our first patient had a prosthetic mitral valve, but her bicuspid aortic valve was responsible for the clinical findings. The second patient clearly had prosthetic valve involvement with heart failure that required valve replacement. Q fever was not initially considered in the differential diagnosis for either person's illness because neither had any history of exposure to farm animals or unprocessed animal products. This has been true for about half of the reported cases of Q fever endocarditis.[1]

The possibility of infection with *C burnetii* must be considered in any patient with clinical features of endocarditis but whose blood cultures are negative. The diagnosis is most easily established by persistently elevated titers of antibodies against both phase I and phase II antigens. Phase I antibodies are produced rarely and only in low titer in an acute, limited infection. According to the World Health Organization expert committee,[1,5] phase I antibody titers greater than 1:200 with clinical evidence of endocarditis are diagnostic of Q fever endocarditis.

Isolation of *C burnetii* from valvular tissue or blood or urine specimens is a hazardous procedure best left to reference laboratories. With the use of special stains, the rickettsiae can be seen in sections of infected tissue and specifically identified by immunofluorescent staining.[6] Attempts to isolate *C burnetii* from frozen valve tissue from the patient in case 2 were unsuccessful. This was most likely due to the fact that he had been treated for nine months before valve replacement was required. Symptomatic response to antibiotics and declining phase I antibody titers had occurred. In contrast, liver granulomas in tissue obtained by biopsy during the acute infection stained intensely (Robert N. Philip, MD, Rocky Mountain Laboratory, written communication, 1978) with the fluorescein-tagged antiserum to *C burnetii*.

Treatment of Q fever endocarditis appears to require prolonged administration of tetracycline.[1,5] The small

*Keith Morton, MD, provided long-term follow-up care.

number of recognized cases and the lack of a sufficient number of cases at any one locale have precluded controlled trials to establish the antibiotic(s) of choice.[1] Long-term administration of tetracycline (for at least 12 consecutive months) with or without lincomycin or trimethoprim/sulfamethoxazole has been favored by some authors as an initial approach, with indefinite treatment recommended if there is evidence of continued activity of the disease.[1,4,5] Our patient in case 1 appeared to respond to short courses of tetracycline on two occasions, but because an allergic reaction developed to the tetracycline, she was maintained until her death from unrelated causes in January 1982 on treatment with trimethoprim/sulfamethoxazole. The patient in case 2 was maintained on antibiotics for 21 months, during which time his bone marrow and liver function returned to normal and all signs and symptoms of active disease disappeared.

Administration of antibiotics preoperatively and long-term postoperatively seems reasonable and should be done to prevent recurrence of the endocarditis from seeding from chronic infection of extravascular tissue, especially from the liver.[1,5]

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Elevated Intramuscular Pressure and Rhabdomyolysis Complicating Streptococcal Fasciitis

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RHABDOMYOLYSIS AND MYOGLOBINURIA compose a well-known clinical syndrome seen in association with various medical diseases including alcohol and drug abuse, seizures, metabolic derangements, hypothermia and viral infections.[1] Similar clinical features accompany the "compartment syndrome," which is well described in surgical articles as occurring following trauma, electrical and thermal injuries, fractures and vascular accidents.[2] We report a case of elevated compartmental pressure and rhabdomyolysis due to spontaneous streptococcal fasciitis.

Report of a Case

A 53-year-old man was admitted to University Hospital (Salt Lake City) because of pain in both arms. He had a history of adult-onset diabetes, hypertension and coronary artery disease, and had undergone saphenous-vein bypass grafting two months earlier. One day before admission the patient had the insidious onset of left calf pain near his saphenous donor site. The next morning he had severe aching pain and swelling in both forearms. He was evaluated at an outlying hospital and noted to be afebrile and normotensive, but to have leukocytosis with a pronounced left shift. Analysis of urine showed 4+ blood and rare erythrocytes. Blood, urine and throat specimens were cultured and treatment was empirically begun with cefazolin sodium given intravenously. He became oliguric and azotemic, producing scant brownish, dark urine. He was transferred to University Medical Center for further evaluation.

On arrival the patient was somnolent and diaphoretic but did not appear to be in distress. The temperature was 36.6°C (98°F), pulse rate 100 and respirations 14. Blood pressure was inaudible, but was detected at 70 mm of mercury systolic by Doppler ultrasound. The right forearm was rigidly held in about 120 degrees of flexion. Active motion was minimal and passive extension of the forearm or wrist elicited exquisite pain. There was significant tenderness and tense swelling centered over the proximal volar aspect of both forearms. He had diminution of pinprick sensation over the volar forearm and hand on the right. Radial pulses were audible by Doppler. Both lower legs showed slight pretibial edema. The left lower extremity had a scar from saphenous vein harvest; distally there was moderate brownish discoloration but no sign of active infection.

Admission laboratory studies disclosed the following values: leukocyte count, 5,700 per μl, with 42% band forms, 53% segmented neutrophils and 4% lymphocytes; hematocrit, 49%; platelet count, prothrombin and partial thromboplastin times were normal; serum sodium, 137, potassium, 3.7, chloride, 100 and total carbon dioxide, 9 mEq per liter; blood urea nitrogen, 50, creatinine, 4.3, glucose, 380, calcium, 8.1 and phosphorus, 5.6 mg per dl, and serum albumin, 3.0 grams per liter. Serum creatinine phosphokinase level was 13,000 IU. Serum lactate level was 8.0 mEq per liter (normal, 0 to 3) with a calculated anion gap of 28. Arterial blood gas determinations made with the patient breathing room air showed a pH of 7.37, a partial arterial oxygen pressure of 73 torr and a partial arterial carbon dioxide pressure of 21 torr. Urine analysis showed 3+ protein, 2+ glucose, no ketones and 4+ blood (Chemstrip 6, Bio-Dynamics Inc, Indianapolis); microscopic examination showed five to seven leukocytes and rare erythrocytes. Urine sodium

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content was 26 mEq per liter with a urine-to-plasma-creatinine ratio of 55. The fractional excretion of sodium was 0.35%. Chest x-ray film and electrocardiogram were unchanged from previous examinations.

The patient was felt to be in shock, presumably due to sepsis, but without a definite source. In addition, he was felt to have compartmental compression of both forearms, rhabdomyolysis and prerenal azotemia. Fluid resuscitation with lactated Ringer's solution was begun and he was given corticosteroids, cefazolin, tobramycin, bicarbonate and mannitol. A Swan-Ganz catheter was inserted. Initial readings showed a pulmonary capillary wedge pressure of 4 mm of mercury. Mixed venous oxygen partial pressure (Po_2) was 34 torr. Cardiac output was 5 liters a minute.

Because of the patient's tense and painful forearms, intramuscular pressures were measured using wick catheters (Myocath, Sorensen Research, Salt Lake City). Initial readings in the right forearm were 45 mm of mercury. Accordingly, volar and dorsal fasciotomies of the right forearm were done. This resulted in expansion of the involved muscles and immediate return of intramuscular pressure to 10 mm of mercury. At the time of decompression the fascia appeared normal, though the subcutaneous tissues were edematous, discolored and somewhat hemorrhagic. Several areas of muscle were pale but regained color on decompression. The forearm wounds were dressed with wet dressings and soaked with 5% mafenide acetate solution (Sulfamylon).

Over the following 24 hours fluid resuscitation was accomplished with about 10,000 ml of fluid. Pulmonary capillary wedge pressure increased to 13 mm of mercury; cardiac output remained about 5 liters per minute. Mixed venous Po_2 remained low at 24 to 29 torr and moderate lactic acidosis (4 to 6 mEq per liter) persisted. Increasing edema developed in the left forearm and anesthesia and paralysis of the wrist and finger musculature. Intramuscular pressure was 45 mm of mercury and decompressive fasciotomy was done. In both upper arms areas of dark skin discoloration developed, associated with the appearance of bullae that contained watery hemorrhagic fluid. Blood and wound cultures done the previous day were all positive for group A β-hemolytic *Streptococcus*. A fascial biopsy specimen taken at the time of fasciotomy showed numerous Gram-positive cocci in clusters and short chains within the collagen fiber meshwork. Antibiotic therapy was switched to penicillin G. Mild diffuse erythema and edema developed in the left leg but no fluid specimen could be obtained for culture.

Over the following 48 hours, the lactic acidosis resolved. The patient suffered an episode of apparent consumptive coagulopathy manifested by prolongation of the prothrombin and partial thromboplastin times, thrombocytopenia, elevation of FR antigen and a fall in his hematocrit to 24%. His fibrinogen level was normal, however, and his bleeding was limited to several small arterial bleeders in the fasciotomies. He was given packed erythrocytes, fresh frozen plasma and platelet transfusions, and the arterial bleeders were ligated. The serum calcium level fell to 5.7 mg per dl with an albumin level of 1.9 grams per dl. He was, therefore, given calcium replacement. Serial electrocardiograms and cardiac isoenzyme determinations showed an acute inferolateral nontransmural myocardial infarction. Because of the possibility of occult muscle damage, a muscle scan using technetium Tc 99m pyrophosphate was done on the fourth hospital day, which showed increased uptake of isotope in the volar aspects of both arms, consistent with the patient's recent fasciotomies. Abnormal uptake of isotope at other sites was not seen.

Although the patient's urine output improved rapidly and was adequate after fluid resuscitation, the serum creatinine level continued to rise, peaking at 5.5 mg per dl, with an associated blood urea nitrogen value of more than 100 mg per dl. Hemodialysis was required for about seven days. Over the following two weeks, the blood urea nitrogen and creatinine levels returned to baseline.

The wounds showed progressive necrosis of fascia and superficial muscle in both the volar and dorsal compartments of the right arm. He was transferred to the burn unit for management of his wounds, which included several operative debridements, homograft dressings and split-thickness skin grafts. He was discharged on the 48th hospital day, at which time the right arm had recovered moderate extension of the elbow and wrist and moderate flexion of the wrist and fingers. Pinprick sensation of the distal forearm and hand had partially returned. Motor and sensory function was essentially normal on the left.

Comment

Streptococcal fasciitis is an uncommon disease associated with diabetes, myxedema, contaminated soft-tissue wounds or an abdominal operation.[3,4] In about a fourth of cases, no antecedent injury can be found.[5] The affected area is warm, erythematous, edematous and acutely painful. The lesion often progresses in 24 to 48 hours to bluish discoloration of the skin followed by serosanguineous bullae formation and full-thickness skin loss.[6] Anemia, thrombocytopenia and hypocalcemia, presumably due to extensive fat necrosis, are frequently seen. Recently several cases of an associated consumptive coagulopathy have been reported.[7]

Therapy for patients with streptococcal soft-tissue infections must have several important goals. First is adequate fluid resuscitation. This patient required ten liters of isotonic solution to restore an adequate blood volume. The use of a Swan-Ganz catheter to guide fluid resuscitation, while not always necessary, is clearly indicated in patients with limited cardiovascular reserve. Appropriate antibiotic therapy must be started early and depend to some extent on empirical broad-spectrum coverage, including penicillin G, until a specific organism is recovered. Many such infections are polymicrobial and involve Gram-negative organisms, *Clostridium* or other anaerobes.[4] Definitive therapy is surgical, with wide debridement and excision of all

devitalized tissue. Despite appropriate therapy, mortality is 16% to 20%, with strikingly higher figures reported in patients with diabetes and those with peripheral vascular disease.[8]

The compartmental syndrome comprises a spectrum of disorders in which muscle and nerve damage result from the compression of tissues within rigid osteofascial compartments of extremities.[2,9-11] The generation of edema within these tissue spaces causes progressive increase in interstitial hydrostatic pressure, producing ischemia and subsequent necrosis of tissues. Compartment syndromes are seen following coma, soft-tissue trauma, thermal burns, electrical injuries, fractures, vascular injuries and iatrogenic infiltrations, especially of vasopressor.[2,9] Classical findings include deep, throbbing pain in the affected extremity, loss of sensory function distal to the site of compression and paralysis of the affected limb in which active or passive motion of distal joints produces exquisite pain. Pulses may be faint or even absent. These symptoms are all relatively late manifestations, however. Often the syndrome begins with mild, nonspecific pain or tingling in the extremities. Measuring intramuscular pressure is of great value in the early diagnosis of this syndrome. Recordings in excess of 30 mm of mercury have been shown to correlate with the eventual development of myonecrosis and nerve damage within compartments, and serve as an indication for decompressive fasciotomy.[10] If done promptly, surgical decompression can result in complete recovery, but if intervention is postponed, irreparable nerve and muscle damage frequently occurs. Following decompression, a conservative approach is advocated with frequent examination of all involved muscle groups and debridement of only obviously necrotic muscle.[4] Skin grafting or closure of skin wounds should be attempted only after an adequate examination to assure viability of underlying structures. Finally, technetium Tc 99m pyrophosphate scanning is a useful tool in identifying areas of damaged muscle, which can be located deep to or absent from the cutaneous wound.[12]

Rhabdomyolysis is a relatively common clinical and laboratory syndrome resulting from skeletal muscle injury with release of muscle cell contents into the circulation.[1] Independent of compartment syndromes, it is seen in a variety of clinical situations including alcoholism, seizures, myopathies, metabolic derangements and influenza-type syndromes. Characteristically, a triad of an elevated serum creatinine phosphokinase level, a strongly reactive urine test for blood (orthotolidine) and pigmented granular casts are seen.[13] A recent review of 87 cases of rhabdomyolysis showed a 33% incidence of acute renal failure. Hypocalcemia occurred in 90% of the patients in whom acute renal failure developed. The degree of serum creatinine phosphokinase elevation bore no correlation to the eventual development of acute renal failure. Correction of volume deficits and the infusion of an osmotic diuretic such as mannitol and alkalinization of the urine with sodium bicarbonate may decrease the incidence of acute renal failure following rhabdomyolysis.[14]

The patient presented here had symptoms of both streptococcal fasciitis and compartmental compression. Because of the patient's relatively late presentation, his course was complicated by significant permanent impairment of motor and sensory function in his right arm. Hypovolemia and hypotension undoubtedly contributed to his nontransmural myocardial infarction and acute renal failure, though he almost certainly suffered pigment-induced renal damage as well.

Although development of elevated intramuscular pressure in association with soft-tissue infection seems logical from a pathophysiologic standpoint, we are not aware of previous cases of this occurring. In one major review of compartment syndromes, infectious causes of compartmental compression have been specifically refuted.[11] Other authors have described the severity and toxicity of streptococcal myositis[15] and the role of anaerobic streptococci in soft-tissue infections,[16] but they have not documented increased intramuscular pressure. In addition, this patient appeared from physical examination at fasciotomy and culture results to have primarily a fascial infection rather than myositis. It is easy to imagine, however, how the propensity for third-space fluid loss that accompanies bacterial infections could lead to constricting edema within rigid muscle compartments. In this setting fluid resuscitation may contribute to the development of intramuscular compression, especially in areas of marginal damage in which compartmental pressure has been shown to increase throughout the period of fluid resuscitation.[17] The gradual development of compression in this patient's left arm would support this idea. In a complicated clinical presentation such as this one, the use of intramuscular pressure monitoring proved valuable in verifying the existence of significant compartmental compression and the need for decompression before the exact cause of the patient's symptoms had become clear.

Patients who have streptococcal fasciitis may initially have confusing diagnostic pictures, as was the case here. Although not previously described, compartmental compression may contribute significantly to the symptoms and morbidity of the disease. Awareness of this relationship and prompt and aggressive therapy remain the elements of successful treatment of these critically ill patients.

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Remotely Controlled, Implantable Versus Manually Controlled, External Insulin Pump

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IMPLANTABLE, remotely controlled insulin infusion systems provide a new approach to insulin delivery in patients who have type I diabetes.[1] To date, only short-term experience (several months) has been reported with their use, and more extensive experience is necessary to assess the possible benefits versus the possible risks.[2-6] In particular, no data have been published comparing the results of an implantable device versus an external insulin pump in the same patient over an extended period of time. This information is urgently needed by internists because within two years several types of implantable devices will be commercially available and diabetic patients will be requesting implantation.

In January 1981 we implanted the first remotely controlled, variable-rate insulin infusion pump into a man with diabetes.[7] Subsequently, Irsigler and coworkers and Mirouze and Selam each implanted a remotely programmable device in a diabetic patient, with short-term success.[8,9] The initial problem we encountered with the implantable system involved reservoir leakage. Following our initial report,[7] no malfunctions were encountered for five months, at which time the batteries in the implanted pump failed prematurely, and this pump was replaced with a pump incorporating an improved electronic design with a potential life span of 18 months. No malfunctions occurred throughout the next 12 months, at which time a comparative trial was begun and an external CPI 9100 (Cardiac Pacemakers Inc, St Paul, Minn) insulin infusion pump with continuous subcutaneous insulin infusion (CSII) was used for the patient. The protocol of this prospective comparison was to maintain the patient on CSII for an additional 17 months, the same period in which the implantable insulin infusion system had been used. After five months, however, the external insulin pump was removed because of recurrent severe hypoglycemic episodes. This comparative study provides insight into the benefits of an implantable versus an external device in the same patient over an extended time.

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Report of a Case

A University of New Mexico insulin pump was implanted in January 1981 in a 41-year-old man with C-peptide-negative diabetes. The implantation procedure has been described in detail elsewhere[7] and involves placing the insulin delivery device within the paraumbilical abdominal wall musculature and inserting a silastic insulin delivery catheter in the intraperitoneal space. The operation requires about 45 minutes and can be done under local anesthesia. Before implantation the patient had had numerous laser treatments for diabetic proliferative retinopathy and many hospital admissions for retinal hemorrhages, on an average of once every nine months for the four years before implantation. Mild peripheral neuropathy was also present. Five months after the implantation the battery of the implanted pump failed prematurely and the pump was replaced in May 1981. The new unit functioned without difficulty for the next 12 months. Then this pump was removed and a CPI Model 9100 external insulin infusion pump was used and a similar basal dosage of insulin was prescribed as with the implanted pump (0.75 to 1.0 units per hour), with bolus doses of insulin at meals equal to 1 unit per each 100 calories of food ingested. The basal rate of insulin delivery was chosen because nondiabetic humans secrete about 1 unit per hour of insulin postprandially.[10] This basal rate was increased or decreased, as necessary, at intervals of two weeks if the prebreakfast blood glucose concentration was consistently above or below 75 to 125 mg per dl, respectively. The quantity of bolus insulin was increased by 33% before breakfast to counteract the "dawn effect" and additional units of insulin were added to each meal dose at the rate of 1 unit of insulin per each 25 mg per dl of blood glucose above 100 mg per dl.[7] Throughout the 22-month crossover study, only short-acting (regular) insulin was used, containing 25 mEq per liter of sodium bicarbonate.

The patient used home blood glucose monitoring before each meal to assess glycemic control. Glycosylated hemoglobin concentration was assayed weekly by the colorimetric method, which expresses the result as total glycosylated hemoglobin. In our laboratory, the 5th to 95th percentile reference interval for a population of 65 nondiabetic persons was 4.6 to 6.1 mol of total glycosylated hemoglobin per 100 mol of total hemoglobin. The range of values for a population of 85 diabetic patients was 6.9 to 20.4 mol per 100 mol of total hemoglobin.[11] Daily records of weight, insulin dosage, premeal blood glucose concentrations and hypoglycemic reactions were kept throughout the study. The patient was interviewed weekly by one of us as to any social problems he may have encountered because of insulin pump therapy. We have previously shown

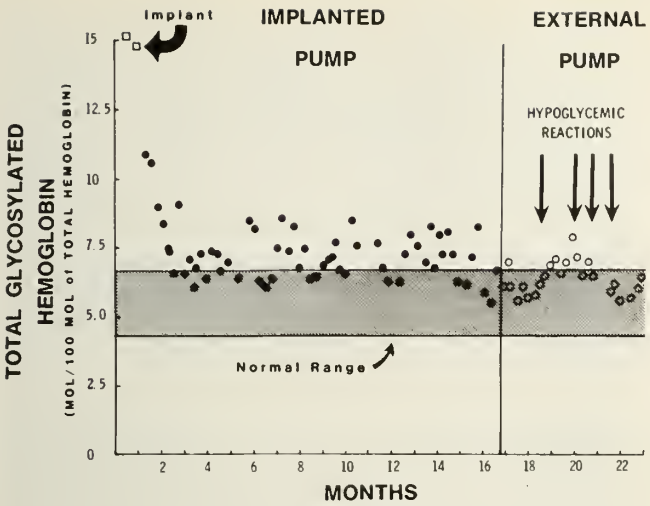

Figure 1.—Total glycosylated hemoglobin (mol per 100 mol of total hemoglobin) throughout a 22-month period during which the patient received insulin from an implanted insulin pump (0 to 17 months) and subsequently from an external pump (17 to 22 months). Measurements were done as an assessment of overall glucose control. The arrows indicate severe hypoglycemic reactions resulting in unconsciousness with blood glucose concentrations less than 40 mg per dl.

that short-term normoglycemia can be achieved with both an implanted intraperitoneal insulin infusion pump and an external subcutaneous infusion pump when a patient is in hospital following a rigid dietary schedule.[7] However, because we believe, as do others,[12] that the risk of hypoglycemia may outweigh the benefits of very tight glucose control in an outpatient setting, the primary goal of this prospective outpatient study was to avert hypoglycemic reactions while improving glycemia and liberalizing the diet. Thus, throughout the outpatient study, the patient followed a liberalized 2,100-kcal diet that excluded only carbonated glucose-containing drinks. No restriction was placed on the timing of meals nor on exercise, though the patient limited himself to mild exercise because of his history of recurrent retinal hemorrhages.

Results

As shown in Figure 1, total glycosylated hemoglobin concentration rapidly declined toward the normal range and remained just above the upper limit throughout the period that the patient was receiving intraperitoneal insulin from the implanted pump. With initiation of CSII, glycosylated hemoglobin concentration decreased slightly into the top portion of the normal range and remained there until the study was terminated. When the mean total glycosylated hemoglobin from the last five months of implanted pump insulin (7.0 ± 0.2 mol per dl) was compared with the mean total glycosylated hemoglobin concentration during the following five months of CSII (6.5 ± 0.2 mol per dl), a significant difference was noted ($P < .05$, Student's t test). Throughout the period of insulin delivery from the implanted pump, the basal insulin delivery rate from the implanted insulin pump ranged from 0.5 to 1.0 units per hour, whereas the basal insulin-delivery rate during CSII ranged from 0.5 to 2.0 units per hour. Meal doses of insulin were similar with both regimens (as described earlier), except that the dose of insulin from the implanted pump was delivered immediately before a meal, compared with 20 minutes before a meal for CSII, because of the more rapid absorption of insulin from the peritoneal cavity.[13] The daily insulin dose during the first month of the implant period was 50 ± 3 units a day compared with 54 ± 4 units a day at the end of 17 months. During the first month of the CSII crossover period, the patient used 52 ± 4 units a day, which he progressively increased so that at the end of five months, 69 ± 6 units a day was being infused. In spite of repeated dietary instruction to limit intake to 2,100 kcal, the patient's weight gradually rose over the 17-month period of insulin infusion from the implanted pump, from 63 kg (138 lb) to 68 kg (150 lb). This weight gain continued during the subsequent five months on CSII, from 68 kg to 72 kg (158 lb).

Throughout the entire 17-month observation period with the implanted pump, no metabolic deterioration occurred. During CSII, however, moderate ketoacidosis developed once following terminal obstruction of the subcutaneous needle through which insulin was being delivered from the external pump. Plasma glucose concentration rarely exceeded 300 mg per dl by either mode of insulin therapy, as assessed by home blood glucose monitoring. However, in contrast to one moderate hypoglycemic reaction requiring the administration of fruit juice during insulin infusion from the implanted pump, four severe hypoglycemic reactions occurred in the early morning hours while the patient was on CSII. These hypoglycemic reactions were associated with seizure activity and incoherence and required the patient's wife to administer first glucagon intramuscularly and then glucose by mouth when the patient had regained consciousness. During the hypoglycemic episodes, blood glucose concentrations were always less than 40 mg per dl as assessed by home blood glucose monitoring using bG Chemstrips (Bio-Dynamics, Indianapolis).

Discussion

In this study we compare the prolonged use of an implanted, remotely controlled insulin delivery system with an external, directly controlled continuous subcutaneous insulin delivery pump in a man with type I diabetes. The implanted system remained in operation for 17 months, during which time reoperation was required once to replace the system because of premature battery failure. Because the external remote controller automatically monitors the function of the implanted pump's batteries, this failure was detected several days before its occurrence, and thus the patient had no metabolic deterioration. During the subsequent five months of continuous use of an external subcutaneous insulin delivery pump, three minor malfunctions occurred, one resulting in moderate ketoacidosis from pump tubing obstruction. The mean total daily insulin dose was greater during subcutaneous insulin delivery, as was the patient's weight, but the total glycosylated hemoglobin was slightly reduced during CSII

compared with that during the period of insulin infusion from the implanted pump.

As assessed by weekly patient interview, one difference between the implanted and the external insulin delivery systems was the degree of social acceptability. From the patient's viewpoint, the implanted system was superior to the external system, both from the standpoint of convenience and from the ability to carry on social interactions. For example, with the implanted system the patient could engage in activities such as bathing without the fear of pump damage or having to interrupt his insulin delivery by removing the pump. Sleeping was also easier, as the patient did not have to be concerned about compressing the pump or dislodging the infusion needle. The fact that he had to have access to an external remote electronic controller with the implantable pump caused little inconvenience as it was easily carried and weighed about 300 grams. The external delivery system functioned satisfactorily throughout the five months as long as the patient paid careful attention to the placement of the insulin delivery needle and changed the tubing at frequent intervals to prevent tubing obstruction by precipitated insulin.

The following two important issues need to be considered: one, the time required to care for a patient receiving insulin from an implanted versus an external insulin pump and, two, the comparative cost of these devices to a patient. Because our experience to date is limited, only estimates can be made. Although initially the care of the patient with the implanted insulin pump was intensive, following his discharge from hospital he required minimal physician time. When use of the external insulin delivery system was begun in this patient, initial care was minimal (he was already educated in home blood glucose monitoring), but with the onset of complications (ketoacidosis and hypoglycemic coma), daily physician monitoring was necessary. More experience is needed before a definitive statement can be made on the comparative time necessary to care for a patient receiving either intensive insulin injection therapy,[14] insulin delivery from an external pump or insulin delivery from an implanted insulin pump. The costs of the two types of devices are also unknown at this time. Although it is probable that the initial cost of an implantable insulin pump will exceed that of an external device with a similar choice of options, if amortized over the lifetime of the device, the total costs may be similar. This is because with implantable devices no disposable supplies are needed, whereas with external devices, new syringes, tubing and needles are required at frequent intervals to prevent infection or obstruction, or both. Until implantable pumps have a functional life span of ten years, however, their total cost (including the surgical procedure for implanting) will probably exceed that of external insulin pumps.

The most significant difference between the implanted and the external insulin delivery devices was the severity of hypoglycemic reactions. With the implanted pump, one episode of disorientation occurred when the patient slept through breakfast and spontaneously awoke before lunch. His hypoglycemia was corrected by ingesting fruit juice administered by his wife. In contrast, the patient had four episodes of severe hypoglycemia in the early morning hours while receiving insulin from his external infusion pump, in spite of repeated instructions on the correct method to prevent this phenomenon. These episodes included seizure activity and required the parenteral administration of glucagon by the patient's wife. These episodes were related to inappropriate elevation of basal insulin delivery by the patient in his attempt to achieve normoglycemia. In spite of repeated instructions not to increase the basal insulin delivery rate above 1.0 units per hour maximum, on several occasions the external pump was placed on 2.0 units per hour background following the evening meal to reduce meal-induced hyperglycemia. The reason the patient increased his basal rate was his belief that normoglycemia would prevent retinal hemorrhage. Although he was counseled that there was no evidence to support his theory, he had been impressed by the fact that he had had no progression of his retinopathy (as assessed by fluorescein angiography) since implantation.

The New Mexico Insulin Delivery System contains an inherent safety feature in that physicians and patients have different external controllers.[1] Patients via their controller can interrogate all of the pump functions, but can make only two changes—that is, start or stop a meal dose of insulin. The patient cannot alter the basal insulin delivery rate. In contrast, a physician's controller not only includes all the functions of the patient's controller, but also provides a choice of 15 different basal rates. These latter functions give a physician total control over a patient's basal insulin delivery.

We conclude that in certain patients, an implanted, remotely controlled insulin device offers safety features not available on external pumps. In our patient, this difference in safety necessitated removing the external pump. Because of his social preference for an implanted insulin delivery device compared with an external device, he has elected to have an improved version of the New Mexico Insulin Pump implanted soon. It should be emphasized, however, that good glucose control was achieved during CSII, and in a patient who does not increase the basal insulin delivery inappropriately, an external insulin pump can provide a similar degree of metabolic control. Thus, the decision of a physician in recommending a particular type of insulin pump must be based on a patient's reliability, safety, financial resources and desire for an improved life-style.

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Enterococcal Endocarditis Following Flexible Sigmoidoscopy

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THE ASSOCIATION BETWEEN lower gastrointestinal (GI) tract endoscopy and bacteremia has been controversial. Studies have shown an incidence of bacteremia following sigmoidoscopy or colonoscopy of 10% to 27%,[1-3] whereas some report that bacteremia occurs in a negligible portion[4,5] or not at all.[6-9] Because of these conflicting data and the absence of a reported case of endocarditis after a lower GI tract procedure, the American Heart Association (AHA) suggested in 1977 that antibiotic prophylaxis be given only for lower GI tract procedures in patients who have prosthetic heart valves.[10] In a recent nationwide survey of endoscopy program directors, however, most did not recommend antibiotic prophylaxis for lower GI tract procedures in any patient.[11] Whether either of these recommendations reflects actual practice habits is unknown.

We have recently become aware of a patient in whom enterococcal endocarditis developed following flexible sigmoidoscopy. We reviewed a local hospital's records and the medical literature for similar cases and surveyed endoscopists, cardiologists and infectious disease specialists in the Denver metropolitan area about their current recommendations for antibiotic prophylaxis in patients with various valvular lesions. In light of these findings, we examined the costs and possible benefits of providing antibiotic prophylaxis to patients with valvular heart disease.

Report of a Case

The patient, a 66-year-old man with compensated rheumatic heart disease (aortic regurgitation and mitral stenosis and regurgitation), was admitted to hospital with painless hematochezia of one day's duration. On that admission a flexible sigmoidoscopy (without biopsy) was done without antibiotic prophylaxis. Internal hemorrhoids were noted, but no bleeding source was identified. Because the bleeding had stopped spontaneously and hematocrit and coagulation values were normal, the patient was discharged in stable condition. Four days later fever, lethargy, generalized weakness and slurred speech developed. The next day the patient was transferred to Rose Medical Center (Denver).

On physical examination at the time of admission he had a temperature of 40°C (104°F). The patient was in a toxic state and was not oriented to place or time. There was no evidence of trauma, papilledema, Roth spots, conjunctival hemorrhages or neck rigidity. There were rales at both lung bases. Murmurs characteristic of aortic regurgitation, mitral stenosis and mitral regurgitation were present. The abdomen was not tender, there was no visceromegaly and a stool specimen was negative for occult blood. Examination of the extremities showed subungual splinter hemorrhages. On neurologic examination he had right upper extremity paresis, right arm and leg hyperreflexia and no pathologic reflexes.

On admission six blood specimens for culture were drawn and within 24 hours all cultures were positive for enterococci. Lumbar puncture showed no evidence of cerebrospinal fluid infection and therapy was immediately begun with ampicillin, 2 grams given intravenously every four hours, and gentamicin sulfate, 80 mg given intravenously every six hours. Subsequent computed tomographic scan of the head showed minimal cortical atrophy but no evidence of vascular or space-occupying lesions. As compared with a prior study, a two-dimensional echocardiogram showed increased echogenicity at the mitral valve that was felt to be vegetations. The patient became afebrile after four days of antibiotic therapy, and no evidence of a noncardiac focus of infection (abdominal, urinary or skin) was found. The patient's abnormal neurologic signs gradually resolved and he was discharged in good health after six weeks of therapy. He has remained well, without evidence of colonic disease.

Methods

After becoming aware of this case, we reviewed all charts at Rose Medical Center for the years 1979 through 1982 that had a discharge diagnosis of bacterial endocarditis. In addition, all records of patients having enterococci cultured from blood were reviewed for the same time period. Rose Medical Center was chosen because the index case was found at this hospital and because it had the highest volume of lower GI tract procedures (sigmoidoscopies and colonoscopies) among area hospitals.

Appreciating that a low frequency complication such as endocarditis would be unlikely to be found by simple chart review and wanting to judge what the current practice habits in the Denver metropolitan area were, we sent a questionnaire to local endoscopists (N=47), cardiologists (N=50) and infectious dis-

(Rodriguez W, Levine JS: Enterococcal endocarditis following flexible sigmoidoscopy. West J Med 1984 Jun; 140:951-953)

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This study was supported by the Kern Research Foundation.
Submitted, revised, November 9, 1983.
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TABLE 1.—*Antibiotic Prophylaxis for Lower Gastrointestinal Tract Endoscopy—Practice Habits in the Denver Metropolitan Area, 1983*

Physician Specialties	Indications for Prophylaxis: Prosthetic Valves Only Percent	All Valvular Diseases Percent	Do Not Give Percent
Endoscopists (N=42)	21	50*	10
Cardiologists (N=36)	11	58	31
Infectious disease (N=10) .	10	50*	30

*The remainder (19% of endoscopists and 10% of infectious disease specialists) give prophylaxis for all valvular disease, with the exception of either aortic stenosis or mitral valve prolapse.

ease specialists (N=15). The endoscopists were asked whether or not they query patients about or examine them for valvular heart disease before doing lower GI tract procedures. All physicians were asked whether or not they (1) "Recommend that antibiotic prophylaxis be given" to no patients who have valvular disease or to those who have any or all of the following: mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, mitral valve prolapse or prosthetic heart valves; (2) give one, two or three doses of antibiotics if they do give prophylaxis, and (3) have ever encountered a case of endocarditis following a lower GI tract procedure. These responses were anonymous and no attempt was made to make certain that the physicians' practice conformed to these recommendations by doing a chart review.

Results

Chart Review

Between 1979 and 1982 there were 18 cases of bacterial endocarditis at Rose Medical Center, and in three cases the offending agent was an enterococcus. In only one case (the index case) could a lower GI tract procedure be temporally related. During the four years reviewed there were 22 cases of enterococcal bacteremia, and in only the index case could a lower GI tract procedure be implicated. A careful search of the medical literature was also unsuccessful in finding additional cases of endocarditis due to a lower GI tract endoscopy.

Physician Survey

The results of the survey of physicians are summarized in Table 1. In all, 42 of 47 endoscopists (89%), 36 of 50 cardiologists (72%) and 10 of 15 infectious disease specialists (67%) responded to the questionnaire. Almost all endoscopists (41 of 42) were concerned enough about this problem to ask about or to examine a patient for valvular heart disease immediately before doing lower GI tract endoscopy. Only a small minority of the physicians who responded would strictly follow the AHA guidelines of prophylactically treating only patients who had prosthetic valves (21%, 11% and 10% of endoscopists, cardiologists and infectious disease consultants, respectively). Most would give antibiotics prophylactically to patients with any type of valvular heart disease, including mitral valve prolapse. Very few endoscopists, but a third of the responding cardiologists and infectious disease specialists, would not give prophylaxis for lower GI tract endoscopic procedures. In light of these practice habits, it is interesting to note that none of the 88 physicians had seen or heard of a case of endocarditis following these procedures.

Of those physicians who would give antibiotic prophylaxis, only 42% of the endoscopists, 56% of the cardiologists and 43% of the infectious disease consultants would recommend the full three doses over 16 hours suggested by the AHA.[11] The remainder are evenly divided between giving one or two doses of antibiotics.

Discussion

We have presented what is probably the first reported case of enterococcal endocarditis following a lower GI tract endoscopic procedure. This happened in a man who had uncomplicated rheumatic heart disease, five days after an atraumatic flexible sigmoidoscopy without antibiotic prophylaxis. This short duration between exposure and endocarditis has been noted with virulent organisms such as enterococci. The neurologic symptoms, possible vegetations seen by cardiac ultrasound study and splinter hemorrhages strongly support the diagnosis of endocarditis. The enterococci strongly suggest a colonic source, with the endoscopy likely causing the initial bacteremia. As rigid or flexible sigmoidoscopy is more widely used to screen for curable colorectal neoplasms,[12] low frequency complications of the procedure may become more apparent. One such complication could be endocarditis.

In the most widely disseminated recommendations about antibiotic prophylaxis,[10] it was noted that lower GI tract procedures "have only rarely, *if ever,* been associated with the development of endocarditis," that valvular heart disease does not require prophylaxis, but that "since the patient with a prosthetic heart valve appears to be at especially high risk, it *may* be wise to administer antibiotic prophylaxis [emphasis added]" and that "this empiric recommendation is based more on concern than on definitive data."

In contrast, the majority of physicians in the Denver metropolitan area who would most likely be consulted about this problem (endoscopists, cardiologists and infectious disease specialists), are recommending antibiotic prophylaxis for all forms of valvular heart disease. We do not believe that the responses we obtained were strongly biased in favor of prophylaxis. On the questionnaire, "None" was presented as an equally acceptable choice and although a statement such as "To whom, if anyone, do you give antibiotic prophylaxis?" might have been more neutral, we wanted to be sure that those who were not cardiologists would address the issues of mitral valve prolapse and prosthetic valves. Whether the physicians' recommendations actually reflect their practice habits cannot be judged from this study. The basis for these recommendations is unclear. A recent survey of gastroenterology program directors[11] indicates that the majority are not giving antibiotic prophylaxis for lower GI tract procedures and are pre-

sumably teaching their fellows to approach the problem in the same way. It is possible that some physicians use prophylaxis because of a concern about possible litigation if endocarditis should develop. Most likely, however, these physicians have concluded that the risk of endocarditis is greater than the costs of giving antibiotics (particularly because most give less than the recommended three doses of antibiotics).

The actual risk of endocarditis developing following lower GI tract endoscopy in a patient who has valvular heart disease cannot be determined accurately. However, the absence of other cases being reported suggests that endocarditis must be rare, if not unique. There are several possible reasons for the rarity of this event. First, the 10% to 27% risk of bacteremia reported by some authors[1-3] is overstated. A more balanced overview of the studies[1-9] that have tried to document bacteremia occurring in such a circumstance is that bacteremia does occur, occurs infrequently, is transient and does not correlate well with surgical manipulation of, or disease in, the colon. Second, bacteria in the portal bloodstream are rapidly and effectively cleared by the hepatic reticuloendothelial system. This would decrease the number of bacteria reaching an abnormal valve. Of the enteric flora, however, the enterococci are highly adherent to endothelium in experimental models,[13] and thus the quantity of bacteria reaching the valve may be of lesser importance. Third, even after dental extractions, a more generally accepted cause of endocarditis, the risk of endocarditis developing when no prophylaxis is given is very small (1.1%).[14] Last, if practice habits across the country mimic those that are currently being recommended in our local survey, then a large portion of patients with valvular heart disease may be receiving antibiotic prophylaxis, which, if effective, might further reduce the risk of endocarditis. Of course, "initial" case reports may lead to corroborative letters of previously unreported cases that may suggest a greater risk. The true risk of endocarditis could be accurately assessed only by a large multicenter prospective study.

The costs (economic, morbidity and mortality) of antibiotic prophylaxis are more easily quantified. It is generally agreed that either ampicillin (1 gram given intramuscularly)—or vancomycin hydrochloride (1 gram given intravenously) in patients allergic to penicillin—and an aminoglycoside (gentamicin, 2 mg per kg of body weight given intramuscularly) are the antibiotics of choice.[10,15] The rationale for three doses of antibiotics (before procedure and at 8 and 16 hours) is that the second and third doses will kill bacteria that are adherent to the damaged epithelial surface. There is little experimental[16] and no clinical evidence that a multiple-dose regimen is more efficacious than a single dose before the procedure. The added cost of the antibiotics in our hospital pharmacy varies from $15 if one dose is given at the time of the procedure to $45 if three doses are given as an outpatient. The added cost of the three-dose regimen might make sigmoidoscopic screening for colorectal neoplasms[12] less cost effective. We have noted several outpatient colonoscopies changed to an inpatient procedure solely because the patient had valvular heart disease, resulting in further costs. The risk of nonfatal drug reactions is about 9% (mostly skin rashes, assuming that three doses of an aminoglycoside have a negligible risk of compromising renal function), and the risk of fatal anaphylaxis from a penicillin is 1 in 50,000.[17] Indeed, if endocarditis is extremely rare, the antibiotic prophylaxis may carry more risk than what it is trying to prevent.

In our view, this case of enterococcal endocarditis following a flexible sigmoidoscopy provides the first clear evidence that there is a finite risk from bacteremia after lower GI tract endoscopy. This strengthens the contention that antibiotic prophylaxis should be used in those clinical situations wherein the consequences of bacteremia would be so devastating that even the remote chance of distant infection could not be tolerated.[10,15] In addition to those who have prosthetic heart valves, we would also give prophylaxis to patients with artificial joints, those on hemodialysis who have arteriovenous shunts and patients who are severely neutropenic, the last because of the risk of septicemia. Until a large prospective study can be undertaken to address this issue, however, the apparent rarity of endocarditis occurring postlower GI tract procedure does not appear to justify the expense and morbidity entailed in administering three doses of antibiotic prophylaxis to all patients who have acquired or congenital valvular disease.

Addendum

Since submission of this article, Rigilano and coworkers reported a case of enterococcal endocarditis occurring after rigid sigmoidoscopy.[18] Their suggestion that flexible instruments may have a lower risk for this complication is weakened by our report.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Less Cutting—More Treating?

To the Editor: What's going on here? The surgical schedule has slimmed down to cover less than one page. No more do I need to wait for two weeks for an early morning slot for elective surgery. Nowadays rarely do the surgical scrub teams acquire any overtime.

There is a steady trend, I believe, toward less rather than more major surgery. Less cutting, more treating. I wonder why?

Are we stinging from being accused of performing "unnecessary surgery"? Are we reacting to peer review—our colleagues peering over our shoulders? Are we realizing that government and third party payors are clamping down on costly surgical procedures? Are the DRGs digging at us?

Surely, all these are contributing factors, but I contend there are other, more significant causes for these changes in surgical practices.

Consider gastric surgery. At one time a posterior gastroenterostomy, the so-called Polya's operation, was the accepted treatment for chronic duodenal ulcer. This gave way to the Billroth I, or the "sleeve resection." This was followed by simple antrectomy, with or without vagus nerve division.

Then, from across the Atlantic, came cimetidine, soon to be joined by sucralfate and ranitidine. These compounds were so successful in the treatment of this disorder that gastric surgery for benign ulcer is now rarely seen on the surgical schedule.

Other surgical techniques have experienced similar changes. Indications for surgery are being narrowed. Radical breast surgery, the Halsted operation we were taught to meticulously execute in no less than three hours, has been replaced by brief and limited surgical procedures, or none at all. Prostatectomy for cancer is considered a secondary option; renal calculi are being pulverized by ultrasound. Diagnostic brain scans have all but eliminated exploratory craniotomy, and patients are asking to have their protruding intervertebral discs liquefied and their gall stones dissolved. The surgical resident does not often get a chance to scrub in on a thyroidectomy done for toxic goiter. Adrenalectomy for metastatic breast cancer has given way to hormonal and chemotherapy.

These are the internal rather than the external causes that are reshaping the very nature of surgical practice. So . . . that's what going on here. Surgery does not stand still but constantly undergoes normal, healthy evolutionary change.

E. R. W. FOX, MD
Coeur d'Alene, Idaho
Special Editor for Idaho

Oral Contraceptives and Six Benign Liver Tumors—The Mestranol Question

To the Editor: We would like to commend Dr J. G. Fitz for his excellent overview "Oral Contraceptives and Benign Tumors of the Liver"[1] and his single case report of the 27-year-old woman whose liver ruptured due to development of a hepatic adenoma ($11 \times 8 \times 8$ cm) when she had been taking norethindrone and mestranol (Ortho-Novum 1/50) for six years. We had two similar cases within the past year, both involving Ortho-Novum products (1/50 and 1/80): The first patient died at age 28, gravida 3, para 2. She had two adenomas ($9.5 \times 7 \times 4.5$ cm—ruptured—and $3.5 \times 2.5 \times 2.5$ cm—unruptured) but had been on a regimen of Ortho-Novum 1/50 for just four years and two months. The case appeared, as did Dr Fitz's case, like a ruptured ectopic pregnancy in the emergency room. The second patient, age 26, gravida 1, para 1, left the hospital with just over 50% of her liver. She also had two adenomas (6×5 cm—ruptured—and $3 \times 3 \times 2$ cm—unruptured) and had taken Ortho-Novum 1/80 for six years and nine months. She also presented to our emergency room with an acute condition of the abdomen and two liters of hemoperitoneum.

We interviewed two other women with liver tumors that decreased in size following cessation of oral contraceptives (Ovulen and Ortho-Novum 2 mg). First, a 37-year-old woman, gravida 2, para 2, had an adenoma of 7 by 5 cm after taking Ovulen for ten years. It was asymptomatic, discovered incidentally during laparoscopic sterilization. It was followed by ultrasound and technetium scans and completely resolved in 21 months. The second was a 32-year-old woman, gravida 2, para 2, with a tumor of 5 by 3.5 cm—having taken Ortho-Novum 2 mg for 12 years—discovered by liver scan done for back pain to rule out cholelithiasis. In two years the tumor has decreased in size to 4 by 3 cm.

We note the reference to "prolonged use of oral contraceptives in patients with hepatic adenomas" and point out the 28-year-old patient who died had used Ortho-Novum 1/50 for just four years and two months.

Dr Fitz's fine article included a lengthy argument for

the association between oral contraceptives and benign hepatic tumors, which is already well documented.[2-4] The question today is not "Do birth control pills cause liver tumors?" but, rather, "Why do liver adenomas occur only in some women?" Do most of these women have a problem demethylating mestranol to ethinyl estradiol? Could a screening method be developed? Methyltestosterone is metabolized with difficulty by the liver and produces creatinuria, as also do 17α-methylandrostenediol and 17α-methylandrostanediol while the esters of testosterone do not have this effect.

It is mentioned that oral contraceptives contain either mestranol or ethinyl estradiol as the synthetic estrogen. We do not agree that there is enough evidence to suggest mestranol and ethinyl estradiol are "equal offenders." The widely quoted study by Rooks and co-workers[5] unfortunately negated a difference between the two estrogens, and this aspect of their work needs further evaluation. Most individual case reports of hepatic adenoma catastrophes, including Fitz's case and ours, continue to involve a history of mestranol use, despite a dramatic steady decrease in the sales of mestranol-containing pills since 1964. It is of interest that no new low-dose oral contraceptive is being manufactured with mestranol.

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Artificial Solutions to Health Care Problems

To the Editor: The editorial "Health Care and Not Enough Dollars"[1] struck a very resonant note. It is indeed unfortunate that our legislators and health care planners cannot understand the simple logic involved. The health-care-pool dollars are indeed finite. Efforts to solve the dilemma by diverting a portion of those precious dollars to advertising to create "competition" (obstensibly to decrease costs) only reduce the number of dollars available to serve patient needs. When businessmen steeped in the Madison Avenue hype and bureaucrats imbued in the concepts of forced competitiveness seek to apply those artificial solutions to health care delivery they fail miserably. The application of those mechanisms only opens the pool of health care dollars to the avarice of those entrepreneurs waiting and lobbying on the sidelines to siphon off large portions of that precious pool.

The real function of advertising is to stimulate a market. If it were not, advertising would not be used by business. It has no other commercial value. Advertising does not in any way create saving. If it did, it would serve no purpose in the commercial world.

Middlemen, those between providers and consumers of medical care, only consume another portion of that finite pool. Their ability to consume has been amply demonstrated. Organizers of many would-be HMOs have displayed their expertise at the old hat trick, causing millions of dollars of federal "start-up funds" to miraculously disappear.

Solutions to the problem of not enough health care dollars must come from the medical community, not from the business community or political arena.

ROBERT E. HOLLIS, MD
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REFERENCE

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Nutritional Aspects of Cross-cultural Medicine

To the Editor: Congratulations are due to you and your guest editor, Dr M. Margaret Clark, for the splendid special issue (December 1983) on cross-cultural medicine. You perhaps realize it could serve as a teaching publication on medical anthropology for students in the health professions and in anthropology alike. I have already commended it to a number of students in both disciplines. The choice of topics and ethnic groups considered is broad enough to be useful to professionals throughout North America and beyond. The impact and excitement of the articles and the feeling of immediacy they impart to the reader are due of course to the authors' own experiences with the patients they are describing and the insights they have thus learned. Nothing could be a better teaching tool.

As a human nutritionist and medical anthropologist specializing in nutritional anthropology I was disappointed, therefore, that discussion of the cultural and behavioral problems arising from differences in diets and food choices of minority groups from those of attending health professionals was not presented with the same sense of personal contact and awareness. Meanings of food to people must be considered in dealing with any health problems in which diet and nutritional status are concerns. Recognizing that these meanings exist and should be worked around in ways similar to treatment of those cultural differences described by the authors in the December issue is essential to mutual respect and understanding, as well as to improvement in diet and health.

There is by now a fairly large body of literature that clearly presents problems of diet change among immi-

grant and other minority groups. These have been written by nutritionists and physicians as well as social scientists, but few of the more pertinent ones are cited in the December article by Freimer and co-workers[1] on nutritional and clinical implications of cultural variation. A few examples may be cited: the work of Casey and Harrill,[2] nutritionists studying food choices of Vietnamese immigrant women in Colorado; the research of Grivetti and Paquette[3] on food choices of first-generation Chinese in California that elicited reasons for preferences for nontraditional foods, and the studies of Bindon[4] on the manner in which Samoan diets have changed with migration from rural to more urban areas of that country and subsequent moves to a western culture (Hawaii). The nutritionist Brewer[5] published a number of reports through the Los Angeles County Health Department of meal patterns and food customs and beliefs of several minority groups in that county, including blacks and Mexican-Americans as well as Samoans.

Some of the references in the paper by Freimer and associates are no longer totally accepted by others (namely, Neel's "thrifty genotype" hypothesis[1(p931)]). The present paper, unfortunately for the person interested in nutritional anthropology, is a superficial and vague treatment of the topic, lacks immediacy (the authors appear to have had little insightful experience of their own with persons of other ethnicities), contains a number of outdated references and is in places incorrect. (There are few cultures, for example, that have not already had some of their own simple carbohydrates[1(p929)].) Even the nutritional explanations offered for phenomena are not clear and concise. I would hope that at a future date some of these deficiencies might be corrected by a report or reports from nutritionists and anthropologists more familiar with this important field and its literature, and with cogent experiences to share with the journal's readers.

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Passive Smoking—Corrections in Tables of April Article

To the Editor: Several typographical errors occurred in Tables 2, 3 and 4 of my recent article on passive smoking.[1] The errors are in the column headed "Deaths Due to Cancer, Percent" in each table.

Table 2 is shown here as it should have appeared. In Table 3, the "Deaths Due to Cancer" percentage for 60 to 69—Smoker should have read 59.3 and for Nonsmoker, 42.9. For 59 and younger—Nonsmoker, it should have read 42.9. In Table 4, the "Deaths Due to Cancer" percentage for 70 to 79—Smoker should have read 25.0 and for Total Group—Smoker 41.8.

Thank you for making these errors known to your readers so that they can make the corrections.

G. H. MILLER, PhD
Edinboro, Pennsylvania

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1. Miller GH: Cancer, passive smoking and nonemployed and employed wives. West J Med 1984 Apr; 140:632-635

TABLE 2.—*Causes of Death in All Women in Relation to Husbands' Smoking History*

Age Group Years	*Husbands' Smoking Group*	*Deaths Due to Cancer Number*	*Deaths From Other Causes Number*	*Deaths Due to Cancer Percent*	*Odds Ratio*	χ^2
80 and older	Smoker	14	150	8.5	1.28	0.27
	Nonsmoker	8	110	6.8		
70 to 79	Smoker	27	87	23.7	0.62	1.24
	Nonsmoker	11	22	33.3		
60 to 69	Smoker	22	20	52.4	0.40	1.99
	Nonsmoker	11	4	73.3		
59 and younger	Smoker	26	13	66.7	4.00	4.21*
	Nonsmoker	4	8	33.3		
Total Group	Smoker	89	270	24.8	1.40	2.18
	Nonsmoker	34	144	19.1		
Median Age	Smoker	68.0	81.0			
	Nonsmoker	71.8	83.4			

*This value is significant at the .05 level of significance.

Second table from Miller article as it should have appeared.

Topics in Primary Care Medicine

Headache—Diagnosis and Effective Management

KENNETH S. PETERS, MD, *Mountain View, California*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN P. McPHEE, MD
Series' Editors

More than 40 million Americans consult physicians each year for complaints of headache. The most common headaches are the muscle contraction (tension) and vascular (migraine and cluster) headaches.

Evaluation

A thorough headache history and complete physical examination focusing on the neurologic components are important to rule out the life-threatening traction and inflammatory headaches caused by brain tumors, cerebrovascular accidents, meningitis and temporal arteritis. Although brain tumor is a very rare cause of headache, a computed tomographic (CT) brain scan should be considered if (1) the history or physical examination suggests neurologic abnormalities, (2) the onset of headaches occurs in a person older than age 50 years or (3) a chronic headache sufferer gives a history of a new type of headache. A CT brain scan is also helpful in evaluating a possible cerebrovascular accident in patients who complain of a new onset of headaches in association with a recent onset of neurologic signs or symptoms. A lumbar puncture should be done in any patient experiencing a headache in association with a stiff neck and fever to rule out meningitis. Temporal arteritis should be considered in elderly patients who have a new onset of temporal headaches in association with proximal muscle pain (polymyalgia rheumatica), jaw claudication or visual symptoms. Careful screening includes palpation of the temporal arteries for the presence of tenderness or the absence of pulse. The erythrocyte sedimentation rate (ESR) is an excellent screening test because 95% of patients having temporal arteritis have an ESR greater than 50 mm an hour.

Diagnosis

Migraine

Migraine headaches usually begin in the teens and 20s and occur in about a 4:1 ratio of women to men. About 65% of migraine sufferers have at least one parent who has migraine, suggesting the importance of genetic factors. The pain is more likely to be unilateral, in the frontotemporal area, and occurs episodically anywhere from two to three times per week to monthly. The pain is usually throbbing but also is described as a piercing or pressure sensation. About 15% of migraine sufferers have auras consisting of scotomata (visual field cuts), photopsia (flashing lights) or paresthesias. Occasionally, the aura persists during the headache phase. The other 85% experience no aura. The presence of associated symptoms such as nausea, vomiting, photophobia, hypersensitivity to odors, noise or movement and diarrhea suggests the diagnosis of migraine.

Muscle Contraction

Muscle contraction headaches are the most common and can occur at any age, but usually occur before the age of 50. The ratio of men to women is about 1:1. The pain is usually located bifrontally or in the occipital area and can occur anywhere from monthly to daily. In severe cases the headache can be constant for several years. The pain is usually described as a viselike, dull, aching or pressure sensation. It usually comes on in the early morning upon awakening or in the late

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afternoon. There is no aura or associated symptom, except for frequent neck or shoulder pain. Many patients suffer mixed headaches, which have characteristics of both the vascular and muscle contraction types.

Cluster Headaches

Cluster headaches occur predominantly in middle-aged men. There is no genetic predisposition. The pain is always unilateral and is usually described as a piercing or lancinating, excruciating, nonthrobbing pain. It is commonly located behind the eye. Associated symptoms include miosis, conjunctival erythema, tearing, flushing of the painful side of the face and nasal congestion. The episodes can occur daily for several weeks, followed by long periods of remission. They usually occur at night and last from several minutes to an hour.

Temporomandibular Joint Syndrome

The temporomandibular joint syndrome can have headache as one of its major symptoms. Other symptoms include jaw tenderness, bruxism and clenching and clicking of the jaw. A physician should listen carefully with a stethoscope for a click, check the alignment of the jaw on opening and closing and palpate the muscles of mastication for any tenderness. The headache can have qualities of either vascular or muscle contraction.

Precipitating Factors

It is important for diagnosis and management to determine any specific precipitating factors for a patient's headaches.

Environmental

Such factors as sun glare, altitude, air pollution, perfumes or changes in barometric pressure can trigger vascular headaches.

Nutritional

For some patients, nutritional factors can play a major role in triggering headaches (see Figure 1). Certain foods containing large amounts of tyramine, an amine derivative, can initiate migraine attacks by causing vascular spasm.

A factor that can differentiate contraction from vascular headaches is the effect of alcohol. If ingestion of alcohol makes the headache worse, there is a vascular component to the headache. If alcohol ingestion makes the headache better, due to alcohol's relaxant effect, the headache is probably muscle contraction in origin.

Other significant foods include monosodium glutamate (MSG), a seasoning found in Chinese food and many processed foods; chocolate, which contains a tyramine-like substance called phenylethylanine (PEA), and caffeine. Caffeine is a double-edged sword. It can be used to abort a headache because of its vasoconstricting properties. Used in excess, however, there is clinical evidence that it can precipitate caffeine-withdrawal headaches. Therefore, caffeine should be avoided except to abort a headache.

Hormonal

Because oral contraceptives can increase the frequency and intensity of migraines, they are relatively contraindicated in migraine sufferers. Very often women will have migraine headaches during or just before the menses.

Postural

Abnormal posture can be a major trigger factor for muscle contraction headaches. Physicians should question such headache sufferers for potential strain they are putting on their neck and shoulder muscles during work. For example, secretaries often turn their head over their left shoulder while typing or bend their heads for extended periods while holding a phone to their ear.

Foods With High Tyramine Content

RIPENED CHEESES

Blue, Boursault, brick (natural), Brie, Camembert, cheddar, Emmenthaler (Swiss), Gruyère, mozzarella, Parmesan, Romano, Roquefort, Stilton

Permissible cheeses: American processed, cottage cheese, cream cheese

MEAT AND FISH

Beef liver, caviar, chicken liver, fish, herring (dried, salted, pickled)

ALCOHOLIC BEVERAGES

Red wine, beer, sherry

VEGETABLES

Avocado (particularly if overripe), fava beans (particularly if overripe)

FRUITS

Bananas, figs (canned, particularly if overripe)

MISCELLANEOUS

Vinegar, sour cream, yogurt

Foods That Dilate the Blood Vessels and Therefore Can Precipitate a Vascular Headache

ALL ALCOHOLIC BEVERAGES

MONOSODIUM GLUTAMATE

Found in Chinese foods, canned soups, frozen dinners, Accent, Lowry's Seasoning Salt, Hamburger Helper, etc.
Check labels of all canned and packaged foods

NITRITE

Hot dogs, bacon, salami, bologna, pepperoni, pastrami, sausages, canned ham

NIACIN

Found in most B vitamin and multivitamins (niacinamide is all right)

Other Foods That Can Cause Headaches

CHOCOLATE

CAFFEINE—EXCESSIVE USE

Coffee, cola drinks, nonherbal teas and some aspirin medications such as Anacin, Excedrin and Midol

Figure 1.—Foods to avoid to prevent vascular headaches.

Psychologic

Psychologic factors also play a major role in triggering headaches. There is a significant incidence of depression in patients who have muscle contraction headaches. Therefore, a careful search for signs and symptoms of clinical depression is indicated. Insomnia with early morning awakening, social isolation, change in eating or bowel habits, cognitive dysfunction and suicidal ideation should be questioned for carefully.

Stress can play a major role in both muscle contraction and migraine headaches. It is very common for migraine headaches to occur in the letdown period after a stressful time is over, such as on weekends or during vacations.

Treatment

In addition to recommendations for reducing trigger factors, the use of abortive and prophylactic medications can be very helpful.

Migraine

Aborting. The ergot preparations are among the most effective medications for aborting migraine headaches soon after they begin. The ergot preparations should be taken as soon as possible once a headache or aura has begun. The best routes include the sublingual in the form of Ergomar (ergotamine tartrate), inhalation in the form of Medihaler-Ergotamine or by rectal suppositories in the form of Cafergot (ergotamine and caffeine) or Cafergot P-B (ergotamine, caffeine, levorotatory belladonna as malates and pentobarbital). Medication taken by mouth, because of decreased intestinal motility during the migraine episode, has a slow onset of action and is therefore not recommended as highly as other forms. Medication given intramuscularly in the form of dihydroergotamine mesylate (DHE 45) can be effective for severe migraine when other routes have failed. Possible side effects of the ergot preparations include myalgias and nausea. The nausea is somewhat dose related and reduced by decreasing the dose of ergotamine used and relieved by giving antiemetics. Ergotism can develop with long-term use, the earliest symptoms of which include paresthesias of the hands and feet with progression to frank gangrene if the dose of ergot preparations is not decreased. Another possible side effect is ergot dependency-withdrawal headache. In this situation, reduction of the ergot preparation often leads to transient increase in the severity of headaches followed by eventual reduction of the headache frequency and intensity. Ergot preparations are contraindicated in patients having Raynaud's syndrome, peripheral vascular disease or coronary artery disease. Isometheptene mucate in the form of Midrin can be used as an alternative to ergot preparations in those patients who experience nausea or cardiovascular side effects. Dizziness and skin rash can occur rarely with Midrin.

There is evidence that the prostaglandins play a role in the migraine process. Some clinical evidence suggests that prostaglandin inhibitors work fairly well for menstrual migraines and for those benign headaches that occur with physical exertion or with orgasm. Aspirin and the nonsteroidal anti-inflammatory agents can be quite effective for reducing milder vascular headache pain.

Once a headache has been ongoing for several hours, more potent, potentially addictive analgesic agents such as butalbital combinations in the form of either Fiorinal (butalbital, aspirin, phenacetin and caffeine) or Esgic (butalbital, caffeine and acetaminophen) are occasionally necessary. Orphenadrine citrate in the form of Norflex or Norgesic (orphenadrine, aspirin and caffeine) can also be quite effective and is nonaddictive. In rare cases, more potent analgesics such as narcotics in the form of codeine or meperidine hydrochloride given intramuscularly are needed. The long-term use of these addictive analgesics should be discouraged by the use of nonaddicting prophylactic agents and by reducing trigger factors. Antiemetics should be given for symptoms of nausea or vomiting. Applying ice to the throbbing pain of the scalp while resting in a dark room can often help reduce migraine pain. If a severe migraine cannot be aborted, a short course of dexamethasone given intramuscularly or by mouth may be helpful.

Prophylaxis. The proper use of prophylactic medications has done much to improve the quality of care for migraine. The β-blockers are the first line of prophylactic agents for the treatment of migraines, having about a 70% response rate. The dosages vary from 80 to 240 mg of propranolol hydrochloride per day. There is clinical evidence that the long-acting and cardioselective β-blockers are also effective as prophylactic agents. For nocturnal and early morning migraine, I have found nadolol or atenolol taken at bedtime to be quite effective. The major side effects of the β-blockers include exercise intolerance, fatigue, insomnia and exacerbation of asthma, congestive heart failure or Raynaud's syndrome. Rarely, diarrhea, nausea or vomiting can occur. β-Blockers are contraindicated in patients who have peripheral vascular disease, heart block or insulin-requiring diabetes.

Cyproheptadine (Periactin) in dosages of 4 to 20 mg a day can also be very effective if β-blockers are ineffective or contraindicated. Increased appetite, weight gain and lethargy are possible side effects.

Methysergide maleate (Sansert) has probably the highest rate of effectiveness for migraine prophylaxis, though its use is associated with frequent and severe side effects. Use for longer than six months can lead to reversible retroperitoneal and heart valve fibrosis. Therefore, a one- to two-month medication holiday is indicated every four to six months, followed by an intravenous pyelogram and possibly an echocardiogram before the medication is restarted. It is wise to begin methysergide treatment at 2 mg taken at bedtime and gradually increase to 2 mg three times a day to avoid common side effects such as nausea, vomiting, palpitations, muscle cramps, drowsiness, hair loss, nasal congestion and sweating. Methysergide is contraindicated

in patients who have peptic ulcer disease as it increases gastric acid secretion and in those who have peripheral vascular disease, coronary artery disease or severe hypertension.

The tricyclic antidepressants (see muscle contraction headache prophylaxis below) have also been clinically effective for prophylaxis of migraine.

If the previously mentioned prophylactic medications for vascular headaches are not effective, the monoamine oxidase inhibitors can be tried. It is very important to educate a patient on avoiding foods high in tyramine because of the risks of severe hypertension in those patients taking monoamine oxidase inhibitors. The most common side effects are postural hypotension and symptoms of excessive central stimulation including trauma, insomnia, hyperhidrosis, agitation, hypomanic behavior and, rarely, convulsions.

Preliminary trials evaluating calcium channel blockers show possible efficacy of these agents in migraine prophylaxis, but more definitive studies need to be done before they are approved for migraine prophylaxis.

Muscle Contraction Headaches

Aborting. Most muscle contraction headaches can be aborted with the use of aspirin, acetaminophen or nonsteroidal anti-inflammatory agents. Occasionally, butalbital-containing preparations can effectively reduce muscle contraction pain. The use of these medicines should be minimized, however, because of their addictive potential. Long-term use of benzodiazepines should be discouraged. Stress reduction exercises, biofeedback and aerobic exercises can be very helpful in reducing muscle contraction headaches.

Prophylaxis. The tricyclic antidepressants have proved to be the most effective prophylactic agents for muscle contraction headaches. One may initiate low doses (10 to 25 mg) of amitriptyline hydrochloride or doxepin hydrochloride and gradually increase as tolerated until therapeutic levels are obtained. Their antiheadache mode of action is probably independent of their antidepressant effects. The common side effects include symptoms due to their anticholinergic effect including blurred vision, dry mouth, constipation and urinary retention. Patients with prostate hypertrophy or glaucoma should not receive tricyclics. Potential cardiovascular side effects include orthostatic hypotension, tachycardia and, rarely, cardiac arrhythmias. Other potential side effects include excessive sweating, fatigue, weight gain and impotence.

Cluster Headaches

Aborting. The ergot preparations have been effective for aborting cluster headaches. Administering 100% nasal oxygen at 7 liters a minute for 15 minutes has also been effective.

Prophylaxis. The most effective prophylactic treatment for cluster headaches is the use of one or a combination of lithium carbonate, methysergide or prednisone. Lithium carbonate is often very effective in divided doses ranging from 600 to 1,200 mg. Blood lithium concentrations should be measured frequently because of the narrow therapeutic-to-toxic dosage ratio. Possible side effects include tremor, lethargy, slurring, blurred vision, confusion, urinary retention and polydipsia. Long-term use can lead to hypothyroidism. Prednisone can also be used if lithium and methysergide are not effective in suppressing cluster cycles. At least a two-week course is necessary, with subsequent rapid tapering. Dramatic improvement is seen most often within the first 24 hours. The initial dosage should be about 60 mg a day.

Biofeedback and stress reduction exercises are helpful in selected patients as adjunctive treatment modalities for migraine and muscle contraction headaches. Temperature biofeedback can effectively control migraine pain. Electromyographic biofeedback and galvanic skin response biofeedback are also effective, especially for muscle contraction headaches.

In summary, an integrative approach involving delineation and avoidance of an individual patient's trigger factors, the proper use of abortive and prophylactic medication and stress reduction and biofeedback in selected patients can be very effective for the management of these common headache disorders.

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Medicine and Government

Local Perceptions of Federal Block Grants

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We report the results of a survey of California county medical societies and county health officers on federal health block grants. Survey respondents agreed that the existing network of health services funded through the federal block grants and the current state-local apparatus for providing these services are sound. Most respondents do not recommend major changes in the service system, and most support a strong state role in administering programs under the block grants.

(Tomfohrde RF, Soman LA: Local perceptions of federal block grants [Medicine and Government]. West J Med 1984 Jun; 140:961-963)

The federal Omnibus Budget Reconciliation Act of 1981, signed into law in August 1981, created a system of block grants to the states to fund many health and social service programs. This legislation combined about 60 formerly separate ("categorical") programs into nine broad block grants, four of which concern health.

The Maternal and Child Health block contains the following formerly categorical programs:

- maternal and child health programs
- Crippled Children's Services
- lead-based-paint poisoning prevention
- counseling and information about sudden infant death syndrome
- hemophilia centers
- genetic diseases testing and counseling
- adolescent pregnancy
- Supplemental Security Income for Disabled Children.

The Preventive Health block consolidates eight:

- rodent control
- fluoridation
- hypertension reduction
- health education and risk reduction programs
- health incentive grants to counties
- home health services
- regional emergency medical services
- rape crisis services.

Included in the Alcohol, Drug Abuse and Mental Health block are the following programs:

- community mental health centers
- drug abuse community services
- drug abuse formula grants to states
- alcoholism treatment programs
- alcoholism formula grants to states.

The Primary Care block contains only two programs:

- community health centers
- primary care planning grants.

Under the block grant approach, federal funds for each block are allocated in lump sums directly to the states, which then establish priorities within each grant area and make funding decisions consonant with those priorities. Primary administrative responsibility and accountability for all programs included in the blocks have shifted from the federal government to the states. As state administrative responsibility for these programs has increased, funding levels have decreased. For example, California lost about 26% of its total federal funds for these programs in the first post-block grant fiscal year. California assumed responsibility for the Maternal and Child Health, Preventive Health and Alcohol, Drug Abuse and Mental Health block grants on July 1, 1982, but has not yet accepted the Primary Care block. (West Virginia is the only state to have accepted the Primary Care block.) In federal fiscal year (FY) 1982, the Maternal and Child Health block lost 25% of federal funds received the previous year for the programs now included in the block. The funds

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for the Preventive Health block were also reduced by 25% and for the Alcohol, Drug Abuse and Mental Health block by 24%. Although federal funds for these blocks remained stable in federal FY 1983, funding has again been cut for FY 1984 for all but the Preventive Health block.

In the context of this reduction in both federal responsibility for and funding of health services, the California Medical Association (CMA) undertook a survey of California counties. CMA initiated a survey of counties to include in its assessment of the impact of block grants the perceptions of people involved in providing health care at the local level. County health officers were chosen for the survey because they were viewed as being knowledgeable about the administration and effect of health block grants. County medical societies were chosen because CMA wanted physicians' perceptions of the block grants.

In the survey recipients were provided with information on the block grants in general and on the amount of federal money previously received by each county for each program now included in blocks. We then asked each recipient questions specific to two of the three health blocks administered by California. In the questions pertaining to the Maternal and Child Health and Preventive Health blocks, recommendations were requested for changes in funding for each block. These included recommendations for shifting funds among programs in each block, whether any programs should be eliminated and why and whether related programs not currently funded through the block grant should be included. County medical societies and health officers were also asked whether or not block grant funds should be selectively targeted at geographic areas and populations throughout the state or allocated directly by some formula to all counties for distribution at their discretion.

Because the allocation of the Alcohol, Drug Abuse and Mental Health block is so specifically laid out by federal legislation, neither states nor counties have much flexibility in distributing the money. Survey recipients were asked what changes or redistribution in the federal allocation formula they would recommend for this block grant, but there were few responses and they are not discussed here. Because the Primary Care block has not been accepted by California, it was not included in the survey.

The surveys for both target groups were essentially the same. County health officers were asked to list their three highest priority programs in each block and to give the county's health budget and total budget. County medical societies were asked if they had been in contact with or planned to contact their county health officers to discuss the health blocks. The survey was mailed in October 1982, one year after creation of the block grant program. All counties and societies were surveyed, with 49% of county societies and 55% of health officers responding. All responses were received by December 1982.

Maternal and Child Health

The responses of both target groups were very similar for all questions concerning the Maternal and Child Health block. In all, 100% of county health officers and 94% of county medical societies recommended continued funding of all programs currently contained in the block. Most respondents recommended against shifting funds among programs in the block—that is, increasing funding for some at the expense of others—and against funding additional maternal and child health-related programs through the Maternal and Child Health block. County health officers named Crippled Children's Services, maternal and child health programs and the adolescent pregnancy programs as their highest priorities in this block.

Both respondent groups agreed that Maternal and Child Health block funds were best administered through selective targeting by the state, rather than by direct distribution to all counties by means of some formula.

Preventive Health and Health Services

Health officers and county physicians also concurred that programs currently funded in the Preventive Health block should continue to be funded (100% of medical societies, 90% of health officers). The health officers were evenly divided on the question of shifting money among programs contained in the block. Those who did recommend shifts in allocations supported an increase in health incentive grants (public health monies that are distributed by formula to all health jurisdictions) and a decrease in rodent control (a program targeted for selected urban areas). Only 29% of the medical societies recommended shifting funds among programs. Most respondents did not recommend funding additional services under this block grant. Health officers listed their three priority programs in this block as health education, health incentive grants and reducing hypertension.

The sharpest contrast occurred in the response of both groups to the question of the preferred seat of administration of the block. In all, 75% of the health officers recommended direct distribution of funds to the counties, whereas 67% of the medical society physicians preferred selective targeting by the state.

Conclusions

A major finding of the survey was the general satisfaction of both respondent groups with the programs included in the blocks and with their administration. Very few respondents in either group recommended major revisions in the programs in either the Maternal and Child Health or Preventive Health blocks.

The strongest differences between the groups appeared in the responses to the question whether the state or the counties should administer the block grant funds. This was particularly true for the Preventive Health block. While the majority of both groups supported selective targeting of Maternal and Child Health funds, the two groups differed greatly on the adminis-

TABLE 1.—*Survey Responses by Densely Versus Sparsely Populated California Counties Regarding Administration of Block Grant Funds*

Responders	Maternal and Child Health Block		Preventive Health Block	
	Direct to Counties Percent	Selective Targeting Percent	Direct to Counties Percent	Selective Targeting Percent
Low-Population Counties*				
County medical society	20	80	13	87
County health officer	44	56	71	29
High-Population Counties†				
County medical society	44	56	38	62
County health officer	60	40	60	40
Survey Average				
County medical society	35	65	33	67
County health officer	48	52	75	25

*Low-population counties represented in county medical society responses are Sierra, Modoc, Mariposa, Plumas, Del Norte, Lassen, San Benito, Lake, Siskiyou and Mendocino. Those represented in health officer responses are: Modoc, Mariposa, Colusa, Plumas, Del Norte, Amador, Tuolumne, Nevada, Mendocino and Kings.

†High-population counties represented in county medical society responses are Santa Barbara, Sonoma, Kern, Ventura, San Mateo, San Francisco, Riverside, Santa Clara, San Diego and Los Angeles. Those represented in health officer responses are: Ventura, San Mateo, Contra Costa, San Francisco, Riverside, San Bernardino, Alameda, Santa Clara, Orange and Los Angeles.

tration of Preventive Health monies: 75% of the health officers recommended direct allocation of these funds to counties, whereas only a third of the medical society physicians recommended this approach.

While county health officers might be expected to recommend increased control of health services in their counties, they seem reluctant to eliminate the state's role in setting policy and priorities. Even when respondents recommended allocation of all federal money to counties, they sometimes cautioned that the state should maintain a strong role. For example, the state should retain responsibility for approving the county's proposed use of federal block grant funds and it should monitor counties to assure that they establish priorities for providing health care to high-risk populations. Other respondents cited specific programs that they view as appropriate for allocation to counties while singling out others that should be targeted to populations at risk.

Some of the less populous counties whose health officers recommended selective targeting commented that theirs are "contract counties"—that is, they contract with the state to administer public health and maternal and child health services. Apparently these counties are not equipped to administer federal block grant money.

Survey responses differed quite a bit among counties with radically different population sizes. The replies from the ten least populated counties and the ten most populated counties represented in the survey show an intriguing variation in responses about how the blocks should be administered. The county society physicians and the health officers from less populous counties show a distinct preference for selective targeting of Maternal and Child Health funds when compared with those counties with large populations (Table 1). The same pattern is generally true for the Preventive Health block, with respondents of less populated counties preferring selective targeting and those of high population counties preferring direct county allocation.

The survey results reflect county opinions in a time of transition for health programs. In general, county society physicians and health officers in both densely and sparsely populated counties are content with the existing system of health services funded with federal block grant money. Respondents lamented shrinking budgets coupled with additional responsibilities, but most agreed that the existing network of services and the state-local apparatus for providing them are sound.

Commentary

Health Belief Systems and the Psychobiology of War

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Belief systems overlie powerful biological and psychological forces that are root causes of war. Much as in medicine where an appreciation of health belief systems is necessary in the control of illness and disease, so the paths to the control of war may lie in an understanding of belief systems and ways to circumvent them. Such understanding gives strong theoretical support to many time-honored but underutilized international initiative and educational ventures. The effort of the medical community to educate the public about biomedical aspects of nuclear war should gain more balance and sophistication with an appreciation of belief systems in the psychobiology of war.

(Elgee NJ: Health belief systems and the psychobiology of war [Commentary]. West J Med 1984 Jun; 140:964-968)

Pronouncements about the end of the world are characteristically met with disbelief. Similarly, attempts to educate the public about the medical implications of nuclear war run up against belief systems. The thesis of this essay is that an appreciation of the significance of belief systems in the psychobiology of war can point to paths around the irrationalities they present and make the education effort more effective.

We know how difficult it is for health education to change behavior in everyday matters like smoking and dieting. Face-to-face counseling and exhortation seldom have the desired effect.[1] Nor does new information in the mass media convert people to new belief systems.[2] Conviction that vitamin megadoses ward off disease can be impervious to criticism while scientific facts meet irrational resistance. There is, however, at least one model of health education showing that adverse health behavior can be favorably influenced across an entire community even in matters of diet and smoking.[1] This requires a large outlay of effort and money and a highly sophisticated design. Such is the level of sophistication we should seek in our efforts at nuclear education. I propose to explore the health belief systems that relate to nuclear war in the light of behavioral science, and from this study to suggest ways of improving our public education effort.

First, some background biology and psychology need examination, notably aggression in primates, pseudospeciation (in-groups/out-groups), the genetic leash on human behavior (sociobiology) and the derivation of belief systems. Then the relation of this basic material to the problem of war will be considered and education in the prevention of mass violence discussed.

Aggressive Behavior in Primates

Although no other primate species makes war as humans do, our closest biological relatives, the African apes, defend territory in organized groups and sometimes cooperating males from one chimpanzee community appear to deliberately provoke fights with other communities of their own species.[3] This cooperative aggression is unusual since in other mammalian species single males defend areas against all other males. Probably the evolution of cooperative behavior in primates is related, in part, to the evolution of aggression.[4] A similar but not necessarily related linkage sees proficiency and cooperation in warfare as a selective advantage in human evolution.[5] Aggressive behavior in humans, between humans and animals, and between human pairs and groups is easily learned, practiced by children and youth in play, and encouraged and rewarded by society.[6]

The likelihood of violence in primates increases when strangers are crowded together, especially in the presence of valued resources. As with human needs, valued and frequently scarce resources include not only

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tangible entities like food and optimal breeding circumstances, but also psychological needs such as status and dominance.[6]

Pseudospeciation

Much more complicated than chimpanzee territorial struggles, the human propensity to subdivide into antagonistic groups is profound and widespread and the distinctions are based in belief systems such as religion and politics. Even in basic categories of tribe, race, nation and language, belief systems relating to the superiority of one group over another are central components of the antagonisms. Erikson points out that the rivalry involves goals beyond biological health and prosperity to dreams of immortality.[7] In this process the in-group sees itself as a superhuman pseudospecies and its adversary out-group as a subhuman and evil pseudospecies. From this concept of pseudospeciation, the subhumans are targets for domination and even genocide.[8] This may help explain the curious fascination of humankind in the injury and killing of other humans and the ease with which such behavior can be rationalized.[9]

The Genetic Leash

It is generally agreed that human social behavior, including aggression, is genetically constrained, but many argue about the extent and importance of that constraint. Some hold that the genetic leash is long, loose and inconsequential[10] but sociobiologists make a strong case that in many areas of complex human behavior, including aggression, the leash can be short and tight, and we would be well advised to know these limits and work within them.[11] Sociobiology draws on population genetic studies in animals and suggests that much as the foundations of modern medicine are built on fruit flies and colon bacteria, so we might learn about aggression and war from studies of creatures like the social insects. There are profound differences, of course, since there is an immense overlay of culture influencing human behavior in contrast with the fixed set of behavioral possibilities that insects inherit. One important example of a fixed insect-like behavioral pattern in humans is the universal display of anxiety of very young children in the presence of strangers. Apart from this type of exception, humans are not "hard-wired" like insects. Instead, we inherit capacities and biases: capacities for certain behavioral patterns and biases to learn one or another of those available. Some behavior, aggression being a good example, is innate since it is easy to learn and hard to overcome.[12] Even though the human repertoire is huge it is bounded by finite genetic limits, and our behavioral biases are those that enhance the perpetuation of those genes best conferring biological fitness on the individual person. With a knowledge of the environmental history of a species the sociobiologist can predict the responses that will be selected for perpetuation. The territorial aggressive behavior of human hunter-gatherers, for example, conforms to ecological theory based on animal studies.[11] Warfare itself is a selective force in human evolution. Groups with the best intragroup ability to cope with attacking groups survive, their genes favored. So our heritage is that of a species primed for war.[5]

Since genetic change proceeds slowly, even accelerated by culture in the gene-culture coevolution theory recently advanced,[13] we tend to behave in ways appropriate to our hunter-gatherer past rather than present circumstance. When we develop phobias, our genetic heritage is wired so that we fear ancient dangers—closed spaces, heights, thunderstorms, running water, snakes, spiders. We do not have phobias about nuclear weapons, guns, autos, explosives and electric sockets. Humans also equate events that have little likelihood of occurrence and little consequence with rare events that can have catastrophic outcomes like warfare. Like nuclear warfare. We equate unlikelihood with inconsequence with unthinkable.[13] This represents a kind of belief system that, like many, incorporates denial mechanisms. Perhaps we have a genetic bias to use such denial systems, making them easy to learn and hard to overcome because they conferred genetic advantage on our kind in ancient times. They certainly do not help now. As Einstein noted early in the nuclear age, we have to change the way we think. This sounds hopelessly utopian. How can we change the way we think? But consider the following: Belief systems, we know from our experience with the health belief model, can be changed. And belief systems are ways of thinking. So there are practical possibilities in Einstein's prescription.

The Roots of Belief Systems

Our ways of thinking—with our belief and denial systems—arise within our self-consciousness, that enigmatic human attribute so close to our very essence. Self-consciousness cannot be imagined as anything less than a sine qua non for human evolution. Yet inextricably bound to it is a counterevolutionary force, for self-consciousness holds within it, pari passu, awareness of death. Knowledge of ultimate extinction holds humankind hostage and afraid, so afraid that we can look at it only through belief systems—religious, scientific or political—and through denial, the universal system as portrayed with penetrating multidisciplinary insight by Becker.[14,15] Health belief systems exemplify the process. Illness and disability are forerunners and reminders of mortality, and health belief systems attempt to circumvent and delay this fate—or deny that it matters. Freud unfortunately dulled our appreciation of denial. Any question of the validity of a Freudian theorem could be dismissed as denial and the question turned on the questioner—a catch 22. Freud came close to the full development of his insight but did not quite appreciate the central problem of the dread of death, which in the nuclear age threatens the very life of the planet. We now face the ultimate catch

22 since the denial of death may be so counterevolutionary as to be lethal.

Death-Denial Belief Systems Make Enemies Necessary

Death denial promotes in-group/out-group divisions of peoples; indeed, it may be the prime reason for pseudospeciation. We attempt to avoid our mortality by getting into safe groups. The religions of the world are prime examples, but modern humans fabricate many institutions to provide a sense of being in a chosen group for self-perpetuation: nations, corporations, revolutionary cells, political ideologies, even scientific societies. All promise power, heroic importance and larger meaning.

The primitive human mind divides the universe into mortals and immortals, the first pseudospeciation. Alliance with the supernatural makes tribal power sacred. Out-groups lack this sacred power. An in-group represents the sacredness of humankind; an out-group, the nonhuman animal side. This process continues unabated as we approach the 21st century: even today our adversary is an "evil empire" (President Ronald Reagan addressing the National Association of Evangelicals in Orlando, Florida; March 8, 1983). To rule the out-group enhances the good and controls evil. Enemies serve a double necessity, enabling us to test our immortality power and purge the world of evil at the same time.[16]

As Kennan says, there is the "need . . . for an external enemy . . . in whose allegedly inhuman wickedness one (can) see the reflection of one's own exceptional virtue."[17] Our tragedy is that we are never satisfied; we are gods with animal bodies, who can never be perfect. So we are always testing our power and purging victims. Lifton describes the process brilliantly in his book on the Chinese revolution.[18] Mao the god-king is the fount of sacred power and those outside the revolution, the nonhuman pseudospecies, imperialistic dogs, class enemies, the tainted ones—they shall be the victims. "We shall smite their dog mouths and our bayonets shall taste blood." Our vulnerability to death causes a struggle for power in which to fortify ourselves and arbitrarily define as evil those struggling to get power over us.

War

From this overview, both biology and psychology see humankind driven to self-perpetuation at the expense of others of our own species. Our need to control and dominate others is deeply rooted. We seek life for our genes and immortality for our souls by showing our superiority over the mortally flawed out-groups. It is psychologically and biologically sound for us to wish heroism for ourselves and our pseudospecies, while trying to rid the world of these evil others. Here, in what Moore calls sacred hatred,[19] lies a cause of war. Our enemies are evil by definition. Until we have power over the competing pseudospecies, even if it takes their extermination, we have not proved our heroic worth. But our situation has drastically changed; in our denial of death and quest for power, nuclear war can exterminate humankind.

Education of the Public About Nuclear War

The medical community is deeply aware of the possibility of nuclear annihilation and feels an intense responsibility to bring to public consciousness the extreme danger of playing with nuclear fire. It is frustrating to then confront the "what do we do now" question, realizing that we are not politicians. Our expertise is only as physicians.[20] But we are students of health belief and denial systems and have some success in surmounting these.[1] Coupled with our basic background in biology and psychology, we are equipped to make our education effort more sophisticated. There are two main components of this enterprise. One is education about belief systems in general and pseudospeciation in particular. The other studies ways to circumvent our denial systems and resolve conflict without resort to mass violence.

Consider, for example, that some of our youth are paralyzed by fear of the end of the world, because they are exposed to unrelieved death imagery. Some understanding of pseudospeciation might engage them in a pursuit of the kinds of skills that would build paths between the pseudospecies. They might, for example, study foreign relations, international trade and law, or learn to speak Russian.

The remainder of the essay will examine approaches like this, how we can circumvent the anachronisms—the irrational reflex aggressions and immortality questings by pseudospeciation—and build structures that resolve conflict without resort to mass violence.

Superseding Pseudospeciation With Superordinate Goals

Can nuclear weapons or, better yet, war itself, be perceived as a common out-group, a common enemy like "The Martians"? This advances the idea of superordinate goals—objectives of supreme importance shared by competing groups who can achieve this common goal only if they cooperate.[4] Two nuclear powers might realize that the risks of their nuclear weapons themselves exceed the threat faced were they both denuclearized and then they might agree to the superordinate goal of denuclearization. A citizenry thoroughly informed of the horrors of nuclear war and the likelihood of extermination could serve such a superordinate cause if both sides participated equally and the dangers of oversaturation with nuclear imagery did not supervene. These dangers are those of disillusion on the one hand, leading to resignation and denial, and, on the other, in the event fascination with war is aroused, of xenophobia, scapegoating and blaming which could even lead to ideas of preemptive first strikes.[4,8] These dangers could be minimized if education in belief systems balanced the effort, but the design and expense of such an undertaking would dwarf any experience we

have with, for example, the health belief and behavior model.[1]

Circumventing Belief Systems by Unilateral Initiatives

There are more modest ways to work our way around pseudospeciation and education can focus profitably on both the basic belief problem and on the approaches suggested by this understanding. We can endorse initiatives that conform to our appreciation of pseudospeciation theory even though the theory itself is not widely known. Prime examples are peace initiatives, independent acts undertaken by a society before agreement with its adversaries, but designed to gain reciprocation from them and thus set the ground for agreement. The initiative act enhances our sense of power and, once underway, puts our adversaries in such a position that joining increases their sense of power and failure to join diminishes it. In 1963 President Kennedy announced, without prior agreement, that the United States would cease atmospheric tests and would not resume them unless the Soviet Union did so first. This initiative led shortly to the Limited Test-Ban Treaty. It worked. Osgood had suggested this approach in 1962, emphasizing that such initiatives, while unilateral, should be graduated, in order to induce reciprocation.[21] Such a graduated process also conforms to pseudospeciation theory in that power and the perception of power remain balanced. Large unbalancing unilateral moves risk dangerous stretching of the genetic leash and cultural constraint. The biological and psychological needs for nationalism and military strength are too deeply embedded to confront directly with indiscriminate altruism.

The depravity of a world stocked with 50,000 nuclear warheads is inspiring what might appear to be naive solutions. One, for example, envisions a superpower dismantling one of its nuclear devices in remote Iceland and the spotlight on that act of power induces a like act in the adversary, the process repeating itself to the eradication of the stockpiles. This suggestion actually is putting pseudospeciation theory to work and is not as naive as a first impression might suggest. Each dismantling act enhances immortality power. The decrement is small enough so the old power stability of "deterrence" is not altered but the reduction in arms moves both pseudospecies away from annihilation. While the proposal exemplified is a caricature, it illustrates the power of the initiative process.

Initiatives would address the arms race in all its dimensions, and would include, for example, establishing uniform military financial accounting so as to create the baseline for percentage reduction in all classes of arms. Initiatives can also address nonhardware questions, such as the necessity of creating political community across national borders: of particular interest to physicians would be information and exchange policies capable of helping diversify and pluralize closed societies. Again, these initiatives are all designed to induce bilateral participation and build structures for resolving conflict.

Recognizable here is the win-win strategy of popular psychology. In a similar vein the art and science of negotiation is under study and a recent book *Getting to Yes: Negotiating Agreement Without Giving In* by Fisher and Ury[22] nicely exemplifies pathways of mastery around pseudospeciation.

Pseudopseudospeciation

Another approach to pseudospeciation turns it against itself, as it were, by encouraging the formation of multiple international pseudospecies. In this way populations are subdivided into groups with various professional, business, scientific and other international loyalties so that they are no longer a discrete, homogeneous single pseudospecies. Wilson[11] and Hamburg[4] suggest that a tangle of such cross-binding ties may be able to confound the genetic bases of our irrational behavior.

International Physicians for the Prevention of Nuclear War is a candidate for such an international cross-cultural linkage for physicians. As presently constituted, it has a single message, the stupendous devastation of a nuclear war and the helplessness of the medical community to heal anything thereafter. Its message could help achieve perception of the prevention of nuclear war as a superordinate goal but as argued above would be strengthened if balanced by a similar commitment to international understanding of pseudospeciation and its belief systems. Were it to acquire such an expanded set of concerns so as to represent a full professional ethic, with positions on other issues as well—such as biological warfare and imprisonment under the guise of treatment—it could develop into an international professional pseudospecies serving supranationalistic goals. An example of the effectiveness of such an organization in the resolution of international conflict is shown by the the role of the airline pilots whose refusal to fly to countries that harbored hijackers helped curb that international blight. By transcending national boundaries in the service of their profession and of global human interest, the pilots were able to act where national governments had failed.

The promotion of multiple and complementary loyalties also makes sense in Becker's schema, in that it encourages a more objective look at our sacred hatreds. This suggests an education effort in our primary and secondary schools to develop what might be called global fundamentals: foreign language proficiency, skills in international affairs and studies of world cultures. One of the side effects of our enhanced holocaust consciousness is a sense of futility and despair in our young people. They can become part of the problem if they are not enabled to see their opportunity—in such foreign studies—to work on solutions. The concepts of contemporary social and biological theory, including pseudospeciation, should be added to the curricula of our higher educational institutions including as well the fledgling US Academy of Peace and

Conflict Resolution. Physicians as citizens have an important responsibility in fostering this kind of education reform.

Education Around the Psychobiology of Aggression

There is a profound genetic bias for humans to learn violence. They start life fearful of strangers and we know from behavior in higher primates that stranger-contact is a powerful instigator of aggression,[4] particularly in crowded circumstances. Hence, efforts to know and understand other people through the development of cross-cultural exchanges and education, trade and foreign language study serve us well. Involvement by physicians in the problems of population control also works at the root causes of war.

Americans lead the world in violent television programming. Health professionals are actively and heavily involved in the attempt to reverse this and enable us to lead internationally toward the portrayal of the nonviolent resolution of conflict.[4] This also is an important professional contribution to the cause of peace.

In the competition for limited resources, aggression is the ingrained ultimate weapon and even in a perfect world of population control and nonviolent media there is one resource that is, in a sense, always limited to but one possessor, namely, who shall rule, whose belief shall reign. Consequently, belief systems will always be in conflict and we will never be free of the danger of mass violence. International law eventually must govern, but meanwhile we must continue to work our way around our biological and psychological propensity to war.

Beyond Beliefs

This view of belief systems suggests two interactive principles to follow in the control of war. One insists that we squarely face the human proclivity for cruelty and destruction and that we subject proposals for remedies to critical review, looking to see that the dynamics of belief systems are accorded full recognition. The other principle, that of democracy, is necessary for the exercise of the criticism. Becker prefaces the final chapter of his great unfinished work *Escape From Evil* with a quote from Ricoeur: "if we can no longer live the great symbolisms of the sacred in accordance with the original belief in them, we can, we modern men, aim at a second naivete in and through criticism."[23] In the service of criticism Becker praises democracy "because it . . . addresses itself to the problem of mystification by the free flow of self-criticism"[16] and concludes that

> the gauge of a truly free society would be the extent to which it admitted its own central fear of death and questioned its own system of heroic transcendence—and this is precisely what democracy is doing much of the time. This is why authoritarians always scoff at it: it seems ridiculously intent on discrediting itself. The free flow of criticism, satire, art, and science is a continuous attack on the cultural fiction. . . .[14]

Yet even the democratic process suffers under nuclear arms. What review does the citizenry have when war declarations provide but a few minutes' response time? It is not a democracy when our President has to have the power of a king.[24] We now have the opportunity, in our second naivete but with some understanding of belief systems, to take some control of our destiny and make the world a saner place for its children.

Addendum

The strength of Freeman Dyson's new book (*Weapons and Hope,* New York, Harper and Row, 1984) comes from his intuitive appreciation of psychobiologic constraints. He does not develop this understanding from the new basic science of man but relies on the old concept of original sin. The power of this metaphor belongs to a former age. When interpreted with the new understanding of denial of death and pseudospeciation, his stories and morals, images and concepts, hold formidable power for the survival of civilization.

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Death in the West – A Regional Analysis of the Youthful Suicide Rate

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A remarkable increase of youthful suicides over the past few years has caused the death rate for 15- to 24-year-old adolescents and young adults to rise while there has been a reduction in mortality for all other age groups.

To analyze the geographic pattern of this youthful suicide epidemic, a national interstate analysis was done for the years 1964 through 1978. Results indicate a broad regional effect with high ratings of youthful suicide concentrated in the western United States, especially among states of the intermountain region.

Statistical analysis shows a strong inverse relationship between youthful suicide and population density. Previous research in this area has usually related high population density (overcrowding) to social and behavioral pathology. The present research indicates, however, that low population density (undercrowding) can also have adverse effects. These undercrowding effects may occur because of social isolation, limited social services and loneliness.

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During the past 20 years there has been an epidemic increase of violent death (accidents, suicides and homicides) among our youth. The Surgeon General has noted that there has been a reduction in mortality for every age group in the country save one. That one exception is the adolescent and young adult segment (15 to 24 years old) of the population.[1(p43)] For this age group the death rate has actually increased over the past 20 years and the increase can be traced directly to the twin factors of suicide and homicide, two modes of death that almost doubled over the ten years from 1966 through 1975.[2] As Table 1 shows, all other leading causes of youthful death have declined; clearly the increased incidence of homicide and suicide has been directly responsible for the overall rise in youthful mortality. A fundamental premise of the epidemiology is that deaths and disorders do not occur at random but that they vary significantly by factors of time, person and place. Identification of these various risk factors is essential for planning resource expenditures, designing preventive strategies and reaching a fuller understanding of the phenomena under investigation. Accordingly, it was decided to investigate whether the increased incidence of youthful suicide has occurred uniformly across the country. Determination, analysis and interpretation of the geographic patterns of youthful suicide formed the primary objectives of the present study.

Method

To understand how the youthful suicide rates vary, to locate where the highest and lowest rates occur and to identify where the greatest increases are taking place, death certificate data were collected from various mortality tables contained in the *Vital Statistics of the United States*.[3] Data were gathered on the incidence of suicide among 15- to 24-year-olds in each of the 50 states and the District of Columbia. The time period for this study was the 15-year interval, 1964 through 1978 (the latest years for which comprehensive mortality data were available). Once the suicide incidence figures were collected for every state for each of the

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15 years I calculated suicide rates using data from the 1970 US Bureau of the Census[4] as the population denominator. Consequently the rates described in this paper are all age-specific, cause-specific, annual rates per 100,000 population. In addition, various summary rates were calculated for the five-year intervals, 1964 through 1968, 1969 through 1973 and 1974 through 1978, and a comprehensive 15-year summary rate for the entire 1964 through 1978 study period. I then analyzed this data base in several ways with the purpose of determining which states had been fueling the national increase in youthful suicide and what factors might contribute to this heightened self-destructiveness.

Results

Data were separately collected for the five-year age groups 15 through 19 and 20 through 24. The rates for the group aged 20 through 24 were uniformly higher than those for the 15- through 19-year-olds, which is to be expected because the incidence of suicide increases with age. However, the relative rankings by state were basically similar for both age groups so that the separate five-year age groups were collapsed to make one ten-year category of 15- through 24-year-olds. Collapsing categories in this manner provides a greater number of cases and a higher degree of reliability for any conclusions that may be drawn from the data. The age-specific rates, rank-ordered for the various states over the 1964 through 1978 study period, can be found in Table 2. The rates range from a high of 25.4 in Alaska to a low of 6.5 in New Jersey. The median value of 9.6 corresponds closely to the national average (mean) of 9.7. Examination of Table 2 indicates a strong geographic pattern to the distribution of youthful suicide. Of the ten states with the highest rates, nine are located in the West. Conversely, of the ten states that have the lowest rates of youthful suicide, all are located east of the Mississippi River.

Once having identified those states with the highest and lowest rates of youthful suicide, the question remains: In which of these high-risk states have the largest increases taken place over the 15-year study period? The ten states that yielded the highest youthful suicide rates over the 1964 through 1978 study period were selected to determine in which of these states the greatest rises of youthful suicide had occurred. The 15-year observation period was divided into three five-year intervals and incidence figures were run for these time periods. The degree of increase was calculated by constructing a ratio of the 1974 through 1978 average suicide rate divided by the 1964 through 1968 average suicide rate to determine the percent rate of increase. These data appear in Table 3, from which several observations can be made. First, there has been a steady upward progression of the youthful suicide rate. In every case, the 1964 through 1968 rates are exceeded by the 1969 through 1973 rates, which in turn are surpassed by the 1974 through 1978 rates. The states that had the highest initial rate of suicide have generally shown the greatest rate of increase; there are some exceptions to the rule, however. For the nation

TABLE 1.—*Leading Causes of Death, Ages 15 to 24, United States, 1966 and 1975**

Causes of Death	Death Rates per 100,000 1966 Rate	1975 Rate	Absolute Change	Relative Change (in %)
Accident	67.1	60.3	6.8	−10.1
Homicides	7.6	13.7	6.1	+80.3
Suicide	6.4	11.8	5.4	+84.4
Malignant neoplasm	8.4	6.8	1.6	−19.0
Cardiovascular disease	5.7	4.4	1.3	−22.8

*From Seiden and Freitas.[2(p202)]

TABLE 2.—*Suicide Rates per 100,000 Rank-Ordered by Each State and District of Columbia, Ages 15 through 24, United States, 1964 Through 1978**

State	Suicide Rate	Rank	State	Suicide Rate	Rank
Alaska	25.45	1	ND	9.51	27
Nev	24.98	2	Hawaii	9.25	28
NM	20.72	3	Ohio	9.13	29
Wyo	18.03	4	Mo	8.70	30
Ariz	17.99	5	Pa	8.60	31
Mont	16.08	6	La	8.56	32
Colo	15.27	7	DC	8.30	33
Calif	14.95	8	Tenn	8.27	34
Idaho	14.54	9	Kan	8.26	35
Vt	13.68	10	Iowa	8.25	36
Fla	12.21	11	Neb	8.06	37
NH	12.03	12	SC	8.05	38
Ore	11.67	13	Ark	7.91	39.5
Utah	11.31	14	Conn	7.91	39.5
Del	10.93	15	NC	7.79	41
Tex	10.92	16	Ind	7.72	42
Mich	10.71	17	RI	7.71	43
Wash	10.70	18	Ky	7.68	44
Me	10.33	19	Mass	7.47	45
Va	10.27	20	Ill	7.44	46
Okla	10.14	21	Ala	6.91	47
Minn	9.97	22	NY	6.69	48
Md	9.77	23.5	Miss	6.67	49
Wis	9.77	23.5	WV	6.65	50
SD	9.60	25	NJ	6.53	51
Ga	9.56	26			
United States National Average				9.68	

*From Vital Statistics of the United States.[3]

TABLE 3.—*Suicide Rates per 100,000 of Ten Leading States, Ages 15 Through 24, United States, 1964 Through 1978**

Leading States	1964-1968 Average	1969-1973 Average	1974-1978 Average	% Increase 1964-1968 to 1974-1978
Alaska	11.2	22.8	42.3	277
Nev	13.6	21.1	40.1	194
NM	11.7	20.4	30.0	156
Wyo	11.0	20.3	22.7	106
Ariz	7.7	16.9	29.4	283
Mont	10.3	14.3	23.6	129
Colo	9.0	16.1	20.7	130
Calif	9.0	17.4	18.5	106
Idaho	6.9	14.3	22.4	225
Vt	10.9	12.2	17.9	64
United States	5.8	9.5	13.8	139

*From Vital Statistics of the United States.[3]

as a whole, the youthful suicide rate more than doubled during this period, rising from 5.8 in 1964 through 1968 to 13.8 in 1974 through 1978, a 139% increase. Of the ten states with high initial suicide rates, five (Alaska, Nevada, New Mexico, Arizona and Idaho) exceeded the national mean increase of 139%. That is, those five states not only had the highest rates of suicide but also exceeded the national average with respect to their rates of increase.

With respect to the geographic distribution of these leading states, they are overwhelmingly comprised of western states. Nine of the ten high-risk territories are located in the West. In particular, the intermountain western region is overrepresented, accounting for seven of the ten states. (There are only eight intermountain western states; the one state not found among the top ten is Utah, which ranks close behind in 14th place.) What do these geographic territories share in common besides their physical location? One pertinent characteristic is their population densities, which tend to be very low. Table 4 shows the nature of this relationship by testing the degree of association between youthful suicide and population density (defined as population per square mile of land area). As the correlation coefficients indicate, there is a substantial inverse relationship between youthful suicide and population density. For all states of the union, the rank-order correlation is −.56 and if one limits the analysis to states with densities of fewer than 57.5 persons per square mile (the average US population density), this correlation increases to −.67. Focusing on the ten states shows a very strong rank-order correlation of −.78 to population density (Table 5).

TABLE 4.—*Correlation Coefficients for Youthful Suicide (Ages 15 Through 24) and Population Density**

Correlations	*All States*	*States With Densities <57.5†*
Number	50	23
Pearson's r	−.36‡	−.65‡
Spearman's ρ	−.56‡	−.67‡

*From Vital Statistics of the United States (suicide rates)[3] and the 1970 Census of Population (population density).[4(p52)]
†US mean population density.
‡$P<.01$.

TABLE 5.—*Suicide Rates and Population Densities, Selected States**

	Youthful Suicide		*Population Density*	
State	*Rate per 100,000*	*Rank*	*Population Per Sq Mile Land Area*	*Rank*
Alaska	25.4	1	0.5	51
Nev	25.0	2	4.4	49
NM	20.7	3	8.4	47
Wyo	18.0	4	3.4	50
Ariz	18.0	5	15.6	42
Mont	16.1	6	4.8	48
Colo	15.3	7	21.3	40
Calif	15.0	8	127.6	14
Idaho	14.5	9	8.6	46
Vt	13.7	10	47.9	32
		Pearson's r	−.45	
		Spearman's ρ	−.78	

*From Vital Statistics of the United States (suicide rates)[3] and the 1970 Census of Population (population density).[4(p52)]

The association is strongest at the extreme values of high and low population density. It is relatively weaker in those states with average densities and is symmetric in nature because low population density is associated with a high youthful suicide rate and, to a lesser extent, high population density is related to a low rate of youthful suicide. About two thirds of the United States fall within density parameters of 21.5 to 380 persons per square mile; of the remaining 16 states, 10 have densities below 21.5 and 6 have densities greater than 380. Eight of the ten low-density states (Alaska, Nevada, New Mexico, Wyoming, Arizona, Montana, Colorado and Idaho) have very high youthful suicide rates (in excess of 14 per 100,000). They are all located west of the Mississippi River. Five of the six high-density states (New Jersey, Rhode Island, Massachusetts, Connecticut and New York) have low youthful suicide rates (fewer than 8 per 100,000 population). These states are all located on the East Coast of the United States. Eight of the ten high-risk youth suicide states are also among the country's ten lowest states with respect to population density (Alaska, Nevada, New Mexico, Wyoming, Arizona, Montana, Colorado and Idaho). The only exceptions to this rule are the Dakotas, which have low density paired with lower than average suicide rates and, conversely, California and Vermont, where high suicide rates are coupled with high and average population densities, respectively. Excepting these few instances, the data show a substantial negative relationship between population density and youthful suicide, a relationship that is most apparent at the extremes of the national population density distribution.

Whereas it is true that states are not the ideal units of analysis for areal relationships, it should be appreciated that these results are not derived from a scattering of individual states but are based on a broad regional effect centered in the western United States and especially pronounced in the intermountain-western region.

Discussion

Interstate analysis of the suicide rate for 15- to 24-year-olds shows that the epidemic increase of youthful suicide is not distributed on a proportional basis. Instead there is a disproportionate number occurring in the western United States, especially in the states of the intermountain region. Many factors distinguish this region of the country—a greater proportion of males, larger Hispanic and American-Indian populations and, historically, patterns of heavy alcohol consumption—all factors that could influence the suicide rate. For the purposes of this article, however, I have focused on the factor of low population density because it has some clinical persuasiveness in terms of theories of social isolation. Moreover, results indicate a twofold relation-

ship. Not only is low density associated with high suicide rates but the reverse is also true—high population density, which has been connected to many other types of social pathology, is associated with low suicide rates. Therefore we have a relationship that fits the criteria for Mill's canons of agreement and difference as well as concomitant variation. Still, because of the various uncontrolled factors such as sex ratio, minority populations and the like, we cannot be certain that population density is causally related to youthful suicide. Bearing that caution in mind, what evidence is there to suggest a substantial link between suicide and population density? Previous interstate analyses have not specifically tested this relationship though Smith[5] did correlate population density to indices of social well-being; however, he reported that the relationship was weak. Wilson[6] did not attempt to relate population density to his state-by-state analysis of quality of life measures.

Quite the contrary, studies of population density and its effect on human behavior have consistently explored the effects of high density and overcrowding. Although most of the research has been based on animal populations, there is some consensus that human overcrowding may have an impact on such social problems as crime, mental illness and disease.[7]

But what of the opposite end of the continuum—low population density and undercrowding? Galle and Gove[8] in their review of the literature on overcrowding, isolation and human behavior could cite only two studies bearing on the ecological relationship between isolation and behavior. Isolation, defined as living alone, is not precisely the same as undercrowding; nonetheless, their study of US cities of more than 50,000 population in 1970 indicated that living alone was a powerful predictor for both suicide and alcoholism. In addition, Allen[9] has reported that suicide rates were highest in isolated rural areas of California. The adverse effects of isolation may be due to lack of integration into social networks, lack of social controls and lack of social support and feedback in an environment that is conducive to withdrawal and that lacks the significant others who might intervene in a crisis situation. This last point is corroborated by clinical practice in that it is an accepted procedure in the treatment of self-destructive persons to alert as many significant persons as possible to the suicidal crisis and to be sure those who are potentially suicidal are in the watchful company of others until their crisis has passed. Allowing a suicidal person to remain alone is absolutely contraindicated because isolation can exacerbate the potential for suicidal behavior.

Although low population density and undercrowding is not the same as residential isolation, there is a definite connection between low population density and the sort of geographic isolatedness that can lead to social isolation. In low-density areas there are long distances between neighbors, between extended family and between adolescents or young adults and their all-important peer groups. The need to travel long distances to visit with friends may require an automobile; moreover, the time spent in travel can place an additional damper on the ability to sustain extensive friendship networks. This can be extremely important for youthful suicide because social isolation has already been designated as an important psychodynamic factor.[10] To the extent that low density limits the ease of interpersonal contact, it weakens the emotional support networks that are so helpful in coping with stressful situations. The negative effects of isolation and loneliness on health and longevity are well documented in Lynch's book, *The Broken Heart*.[11] Suffice to say that the boomtown rootlessness and residential mobility that can lead to loneliness are more characteristic of the West than any other region of this country. In addition to the way low density may affect interpersonal stress, it can also compound these problems by reducing accessibility to social agencies and treatment services because low-density areas are frequently underserved by social agencies.[12] The manner in which these features might interact has been described by Shore, Bopp, Waller and Dawes,[13] who describe how the lack of referral facilities, geographic isolation and scarcity of telephones pose barriers to the effective delivery of crisis services on Indian reservations. In other words, both extremes of the population density range may have an effect on social and behavioral pathology. High-density overcrowding seems to influence crime and disease whereas low-density undercrowding appears to be related to suicide and alcoholism rates.

Given a relationship between population density and youthful suicide at an interstate level, more intensive analysis at intrastate levels of rural-urban differentials, variations by county, Standard Metropolitan Statistical Area (SMSA) figures and even census tracts might prove helpful in specifying the dynamics of this phenomenon. Analysis of suicide by particular method could determine whether or not the use of firearms—a highly lethal method—may be relatively overrepresented in the West where guns abound. These more specific studies would help to avoid the pitfalls of drawing conclusions about individual clinical behavior from large-scale aggregate data—that is, relationships at the aggregate level may not necessarily hold for individual behavior, a logical problem described as the ecological fallacy.[14] However, a recent study by Gove and Hughes[15] has found that ecological data *can* be used to understand behavior at the individual level. They specifically tested the proposition that social isolation (living alone) was related to death by suicide and alcoholism and concluded that there was a causal relationship between these factors. Their conclusion supports the findings of this study that social isolation and suicide are solidly linked, though it cannot be concluded that the relationship is necessarily a causal one on the basis of this initial research study.

Conclusions

Youthful suicides are most prominent in the western United States and particularly in the intermountain

region. Among its other distinctions, this is a region of low population densities, and in this study an inverse relationship between population density and youthful suicide at the interstate level has been noted. One cannot be certain that this is a truly causal relationship because of a number of uncontrolled variables, such as alcohol consumption, sex ratio and Indian population, that may be related to both suicide and low population density. The contributory effects of these factors must be evaluated in future research. Still, the relationship between suicides and isolation appears plausible. The few ecological studies on the subject suggest that insufficient density may have deleterious effects on human behavior, and we can safely conclude that undercrowding deserves more research attention than it has received. As results of this study seem to indicate, one can be lonely in a crowd but loneliness is more of a problem in those wide open spaces.

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In Memoriam

California Medical Association

Brown, Edgar C., San Francisco. Died February 25, 1984, in Sausalito, aged 58. Graduate of Southwestern Medical School of the University of Texas, Dallas, 1951. Licensed in California in 1955. Dr Brown was a member of the San Francisco Medical Society.

Campbell, James V., Oakland. Died March 3, 1984, aged 86. Graduate of the University of Michigan Medical School, Ann Arbor, 1925. Licensed in California in 1930. Dr Campbell was a retired member of the Alameda-Contra Costa Medical Association.

Custer, Lawrence R., San Francisco. Died February 19, 1984, in Sonoma, aged 83. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1926. Dr Custer was a retired member of the San Francisco Medical Society.

Easter, George D., Los Gatos. Died March 20, 1984, in Los Gatos, aged 55. Graduate of the University of California Medical School, Berkeley-San Francisco, 1953. Licensed in California in 1954. Dr Easter was a member of the Santa Clara County Medical Society.

Fletcher, Russell, Greenbrae. Died March 7, 1984, in Greenbrae, aged 84. Graduate of Harvard Medical School, Boston, 1926. Licensed in California in 1927. Dr Fletcher was a retired m mber of the Marin Medical Society.

Gordon, Charles F., Perris. Died February 13, 1984, in Riverside, aged 62. Graduate of Meharry Medical College, Nashville, 1947. Licensed in California in 1954. Dr Gordon was a member of the Riverside County Medical Association.

Lewis, Joel Edward, Berkeley. Died March 2, 1984, in San Leandro, aged 72. Graduate of Howard University College of Medicine, Washington, DC, 1940. Licensed in California in 1946. Dr Lewis was a member of the Alameda-Contra Costa Medical Association.

Lucia, Salvatore Pablo, San Francisco. Died March 31, 1984, in San Francisco, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1931. Dr Lucia was a member of the San Francisco Medical Society.

McGovern, Teresa, San Jose. Died February 10, 1984, in San Jose, aged 82. Graduate of the Medical College of Pennsylvania, Philadelphia, 1929. Licensed in California in 1954. Dr McGovern was a retired member of the Santa Clara County Medical Society.

Marcus, Elias George, Glendale. Died February 15, 1984, in Glendale, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Dr Marcus was an associate member of the Los Angeles County Medical Association.

North, Francis S., Palo Alto. Died February 9, 1984, in Palo Alto of amyotrophic lateral sclerosis, aged 70. Graduate of Columbia University College of Physicians & Surgeons, New York, 1941. Licensed in California in 1948. Dr North was a retired member of the Santa Clara County Medical Society.

Rider, Harmon Elliott, Oakland. Died March 26, 1984, in Walnut Creek, aged 70. Graduate of the University of Nebraska College of Medicine, Omaha, 1942. Licensed in California in 1954. Dr Rider was a retired member of the Alameda-Contra Costa Medical Association.

Slattery, Paul Arthur, Orinda, Died January 28, 1984, in Orinda of heart disease, aged 65. Graduate of the University of Rochester School of Medicine and Dentistry, 1943. Licensed in California in 1949. Dr Slattery was a member of the Alameda-Contra Costa Medical Association.

Temple, Ruth J., Los Angeles. Died February 8, 1984, in Los Angeles, aged 91. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1918. Licensed in California in 1918. Dr Temple was an associate member of the Los Angeles County Medical Association.

Torbert, Harold C., La Jolla. Died February 27, 1984, in La Jolla, aged 80. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Dr Torbert was a retired member of the San Diego County Medical Society.

Tucker, Andrew L., Riverside. Died March 20, 1984, in Riverside, aged 59. Graduate of the University of Southern California School of Medicine, Los Angeles, 1948. Licensed in California in 1949. Dr Tucker was a retired member of the Riverside County Medical Association.

Woelfel, Gerard A., Anaheim. Died in March 1984, aged 65. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1943. Licensed in California in 1944. Dr Woelfel was an associate member of the Orange County Medical Association.

Utah State Medical Association

Kiger, Roger S., Salt Lake City. Died February 19, 1984, in Salt Lake City, aged 62. Graduate of Bowman Gray School of Medicine, Winston Salem, 1945. Licensed in Utah in 1951. Dr Kiger was a member of the Utah County Medical Society.

Sundwall, Val, Salt Lake City. Died February 24, 1984, in Salt Lake City, aged 77. Graduate of Washington University School of Medicine, St Louis, 1931. Licensed in Utah in 1931. Dr Sundwall was a member of the Salt Lake County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

HYPOGLYCEMIA: FACT OR FAD?—WHAT YOU SHOULD KNOW ABOUT LOW BLOOD SUGAR—Lynn J. Bennion, MD, Member of the Clinical Faculty, Stanford University School of Medicine, Stanford, California. Crown Publishers, Inc., One Park Ave., New York, NY 10016, 1983. 176 pages, $12.95.

Hypoglycemia is a syndrome with many different causes and about which much misinformation has been published in the popular press. The prevalence of this diagnosis varies among different locales—for example, more patients are diagnosed as having this syndrome in the United States than in Europe, and within the United States, there are more cases in California and New York than in the Midwest. Its incidence seems to correlate with the frequency in which oral glucose tolerance tests are prescribed, the amount of external stress to which people are exposed and the availability of numerous pamphlets and books which misinform the public on the "epidemic" of hypoglycemia.

The author of this book, Dr Lynn Bennion, combines an excellent background in scientific research at the National Institutes of Health with extensive experience as a practicing physician who is presently on the clinical faculty of the Stanford University School of Medicine. In this volume of 176 pages, which is directed to patients as well as health professionals, Dr Bennion has performed a valuable service in defining hypoglycemia and describing its clinical manifestations and pathogenesis with consistent clarity. He outlines its diagnosis and treatment in a lucid and interesting manner, interposing illustrative and memorable clinical cases to highlight the various causes of hypoglycemia and their proper management. The overall result is a text that is readily understandable by nonscientists, yet whose thoroughness and accuracy deserves respect by physicians and even specialists in this field.

I must admit that my initial reaction to reviewing yet another book on hypoglycemia was hardly enthusiastic despite glowing endorsements on the jacket cover by a physician as eminent as Dr Vincent Marks of Surrey, England, whose pioneer clinical observations on hypoglycemic disorders are second to none in this field. However, it became quickly apparent that this was not just "another book" on the subject. Its scope is broad, covering the most common clinical forms of hypoglycemia as found in patients with diabetes mellitus receiving insulin therapy or patients who drink alcohol in the fasting state as well as the rarer endocrine causes of hypoglycemia such as insulinoma or insufficiency of the pituitary-adrenal axis. The author's vivid and realistic description of the discomfort of the glucose tolerance test to most patients and the perspective he provides on the interpretation of this test in diagnosing hypoglycemia is one of the major assets of this book. He reiterates what others have also emphasized concerning the disservice that is done by overdiagnosing hypoglycemia. However, he also warns against an overreaction by some physicians to denunciation by experts against overdiagnosis of hypoglycemia, in that they tend to deny its existence and may thereby fail to diagnose potentially life-threatening hypoglycemia due to an insulinoma.

The author may have overreached a bit in certain chapters, such as when he named his patient "Mrs Sherry Tippler" to illustrate a case of alcoholic hypoglycemia, or when he used a full page figure to depict the analogy of glucose tolerance testing with a college student given $10,000 from grandparents who are trying to determine if he has "hypoprosperity."

Overall, however, the book presents an excellent overview of a syndrome about which much has been written, but seldom so clearly and with such accuracy. It can be recommended to patients as well as to physicians or other health professionals. Its retail price of $12.95 is less than the cost of a single blood sugar test in most commercial laboratories while adding many dimensions of meaning to the understanding and interpretation of that test.

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* * *

WATSON-JONES FRACTURES AND JOINT INJURIES—2 Volumes: 6th Edition—Edited by J. N. Wilson, ChM, FRCS, Consultant Orthopaedic Surgeon, Royal National Orthopaedic Hospital, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 1,280 pages, $175.00.

This new edition will cause nostalgic stirrings in the memories of those orthopedists who trained in the decade following World War II. The reader is aware of the significant presence of Sir Reginald throughout the two volumes even though the presented material is garnered and delivered by a significant number of more current authors. The editor has attempted with some success to develop a sense of togetherness of these different sections, but the style and content as presented by the various authors makes this an impossible effort.

The physical quality and appearance of these volumes are unusually good. The binding and production are of top quality. The print, paper and format are planned for rapid and easy reading with minimal fatigue. Most of the illustrations are effective and beautiful. This is especially true of the paired photograph with drawings which clearly present the intended pictorial message. Many illustrations are of the more traditional type for modern textbooks, and some are uniquely of ancient origin or of limited talent not in keeping with the rest of the production. There is also some tendency to scatter these illustrations in the book in such a manner that they do not fit the page or the text and consequently lose some of their effectiveness.

The general content of the various sections is well organized and well written. There is very broad coverage of most subjects and aspects of fracture and joint injuries but at the same time there is a considerable variation as to the depth and detail of the discussion. There is also a question of timeliness of some sections, such as that written by Watson-Jones. This is beautifully constructed and well worth reading but must be considered in light of more recent information and developments. Unfortunately, there is an occasional abruptness, which presents readers with a void in further information relating to that particular subject.

In general this book is not suitable for physicians as a quick reference. It would be appreciated by mature, practicing orthopedic surgeons for their libraries.

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Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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INFORMATION FOR PATIENTS. Advise patients on **Wytensin** to exercise caution when operating dangerous machinery or motor vehicles until it is determined they do not become drowsy or dizzy Warn patients that tolerance for alcohol and other CNS depressants may be diminished Advise patients not to discontinue therapy abruptly

LAB TESTS In clinical trials, no clinically significant lab test abnormalities were identified during acute or chronic therapy. Tests included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test During long-term use there was small decrease in serum cholesterol and total triglycerides without change in high-density lipoprotein fraction In rare instances occasional nonprogressive increase in liver enzymes was observed, but no clinical evidence of hepatic disease

DRUG INTERACTIONS **Wytensin** was not demonstrated to cause drug interactions when given with other drugs, e.g , digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, potential for increased sedation when given concomitantly with CNS depressants should be noted.

DRUG/LAB TEST INTERACTIONS No lab test abnormalities were identified with **Wytensin** use

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY No evidence of carcinogenic potential emerged in rats during a two-year oral study with **Wytensin** at up to 9 5 mg/kg/day, i e , about 10 times maximum recommended human dose In the Salmonella microsome mutagenicity (Ames) test system, **Wytensin** at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture In another eukaryotic system, *Saccharomyces cerevisiae*, **Wytensin** produced no activity in an assay measuring induction of repairable DNA damage Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9 6 mg/kg), suggesting impairment of fertility Fertility of treated males (9 6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy

PREGNANCY Pregnancy Category C WYTENSIN® MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN A teratology study in mice indicated possible increase in skeletal abnormalities when **Wytensin** is given orally at doses 3 to 6 times maximum recommended human dose of 1 0 mg/kg These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits However, increased fetal loss has been observed after oral **Wytensin** given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg) Reproductive studies in rats have shown slightly decreased live-birth-indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6 4 and 9 6 mg/kg There are no adequate, well-controlled studies in pregnant women. **Wytensin** should be used during pregnancy only if potential benefit justifies potential risk to fetus

NURSING MOTHERS Because no information is available on **Wytensin** excretion in human milk, it should not be given to nursing mothers

PEDIATRIC USE Safety and effectiveness in children less than 12 years of age have not been demonstrated, use in this age group cannot be recommended

Adverse Reactions: Incidence of adverse effects was ascertained from controlled clinical studies in U S and is based on data from 859 patients on **Wytensin** for up to 3 years There is some evidence that side effects are dose-related Following table shows incidence of adverse effects in at least 5% of patients in study comparing **Wytensin** to placebo, at starting dose of 8 mg b i d

Adverse Effect	Placebo (%) n = 102	**Wytensin** (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20% Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less Cardiovascular—chest pain, edema, arrhythmias, palpitations Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort Central nervous system—anxiety, ataxia, depression, sleep disturbances ENT disorders—nasal congestion Eye disorders—blurring of vision Musculoskeletal—aches in extremities, muscle aches Respiratory—dyspnea Dermatologic—rash, pruritus Urogenital—urinary frequency, disturbances of sexual function Other—gynecomastia, taste disorders

Drug Abuse and Dependence: No dependence or abuse has been reported.

Overdosage: Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic Vital signs and fluid balance should be carefully monitored Adequate airway should be maintained and, if indicated, assisted respiration instituted No data are available on **Wytensin** dialyzability

Dosage and Administration: Individualize dosage A starting dose of 4 mg b i d is recommended, whether used alone or with a thiazide diuretic Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response Maximum dose studied has been 32 mg b i d , but doses this high are rarely needed

How Supplied: **Wytensin** Tablets, 4 mg and 8 mg, bottles of 100

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(Continued from Page 893)

June 29-30—**Pediatric Ophthalmology for the Pediatrician and Primary Care Physician.** See Pediatrics, June 29-30.

July 1—**Eureka Clinical Conferences.** UCSF at Eureka. Sunday.

July 7-8—**Weekend with the Masters.** UCSD and Great Teachers Foundation at Double Tree Inn, Monterey. Saturday-Sunday. 20 hrs. $325. Contact: PO Box 61203, DFW Airport, TX 75261. (214) 659-4590.

July 10-12—**Family Practice Board Review Course.** UCSF. Tuesday-Thursday. 22 hrs. $300.

August 1-4—**Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday.

August 17-19—**Nutrition, Obesity, and Weight Control—White Water Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 20-24—**CRYO '84: Course of Freezing of Animal Cells, Tissues and Organs.** UCD. Monday-Friday.

September 1—**Medical Mycology.** UCSF. Saturday.

September 1-2—**Thyroid Today—1984: 3rd Annual Symposium.** Cypress Foundation and Monterey City Medical Society at Doubletree Inn at Fisherman's Wharf, Monterey. Saturday-Sunday. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

September 8-9—**Dermatopathology Board Review.** UCSF. Saturday-Sunday.

September 13-14—**Intensive Course in Adolescent Obesity.** UCSF. Thursday-Friday. $135.

September 17-19—**Relational Issues of Addiction: Violence, Sexuality and Intimacy.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, Conf. Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

September 17-21—**Office Procedures.** UCSF at

Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

September 19-21—**State of the Art in the Care of Geriatric Patients: Pre-Intra-Post-Operative Management.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $325. Contact: Robin B. Jackson, Office of Cont. Ed., PO Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

September 19-23—**Annual Scientific Program and Postgraduate Course of the Pacific Coast Fertility Society** at Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

September 20-23—**34th Annual Obesity and Associated Conditions Symposium.** American Society of Bariatric Physicians at MGM Grand Hotel, Reno. Thursday-Sunday. 17 hrs. Contact: Randall B. Lee, Exec. Dir., 4730 E. Caley Ave., Ste. 210, Englewood, CO 80111. (303) 779-4833.

September 21—**Dermatology and Dermatologic Office Procedure Workshop.** CME at Kona Kai Club, San Diego. Friday. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 23—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. $175. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 29—**Food Allergy: Update 1984.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Geri Coldewey, LASACI, 1626 North Wilcox, #557, Hollywood 90028.

October 1—**Nutrition Symposium.** UCSF at Yosemite. Monday.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Tuesday.

October 8-19—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

October 11-14—**A California Conference in Applied Clinical Geriatrics.** UCD at Napa Valley. Thursday-Sunday.

October 12-13—**Skin From A to Z.** UCSF. Friday-Saturday.

October 12-13—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $200.

October 16-18—**Primary Medical Care of Selected Infectious Diseases.** Health Science Seminars of UCSF at Sheraton Hotel, Poipu Beach, Kauai, HI. Tuesday-Thursday. $225. Contact: Cynthia Vaughan, Program Coordinator, PO Box 22023, San Francisco 94122. (415) 861-2713.

October 17—**Second Annual Alcohol & Drug Dependencies Symposium.** Kaiser Permanente Southern California at The Pasadena Hilton, Pasadena. Wednesday. $90. Contact: Judy Harrison—Dept. of Clinical Services, Kaiser-Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 19-21—**Medical Mycology.** UCSF. Friday-Saturday.

October 29-November 1—**Interstate Postgraduate Medical Association Meeting** at Las Vegas. Monday-Thursday. Contact: H. B. Maroney, Exec. Dir., PO Box 1109, Madison, WI 53701. (608) 257-6781.

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June 23-27—**Ethics at the Edges of Life.** University of Washington School of Medicine at Elkhorn, Sun Valley. Saturday-Wednesday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

July 7-13—**Updates in Trauma: An EPIC Medical Adventure.** Bicycle Tour through the Rocky Mountains, beginning in Sun Valley. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

July 25-28—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday.

Contact: IMA, 407 W. Bannock St., PO Box 2668, Boise 83701.

August 5-11; 12-18—**Computers in Professional Practice: An EPIC Medical Expedition.** Tyrolean Lodge, Sun Valley. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 15-21—**Updates in Pediatrics: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 18-19—**Trauma Update—84.** North Shore Convention Center, Lake Coeur d'Alene. Contact: Linda Ady, Conf. Coordinator, Idaho EMS System, 450 W. State St., Boise 83720. (208) 334-4245.

September 9-14—**Up-to-Date Cardiac Therapy: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. Sunday-Friday. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 18-24—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** Fishing and Chukar hunting adventure on the Main Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

September 21-22—**American College of Physicians—Regional Meeting.** Heritage Inn, Great Falls. Friday-Saturday. Contact: Warren D. Bowman, Jr, MD, Billings Clinic, Box 2555, Billings 59103.

October 4-6—**Montana Medical Association Annual Meeting.** Sheraton, Billings. Thursday-Saturday. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (500) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 21-23—**4th Annual Emergency Medical Services Conference.** Albuquerque. Thursday-Saturday. Clarion-Four Seasons. Hour for hour credit—AMA Cat. I, NM Cat. IV. Contact: C. Thompson, EMS Bureau, PO Box 968, Santa Fe 87504. (505) 984-0024.

June 22—**Medical Control Symposium.** Albuquerque. Friday. Clarion-Four Seasons Hotel. 6 hrs. NM Cat. IV. Contact: Emergency Medical Services Bureau, PO Box 968, Santa Fe 87504.

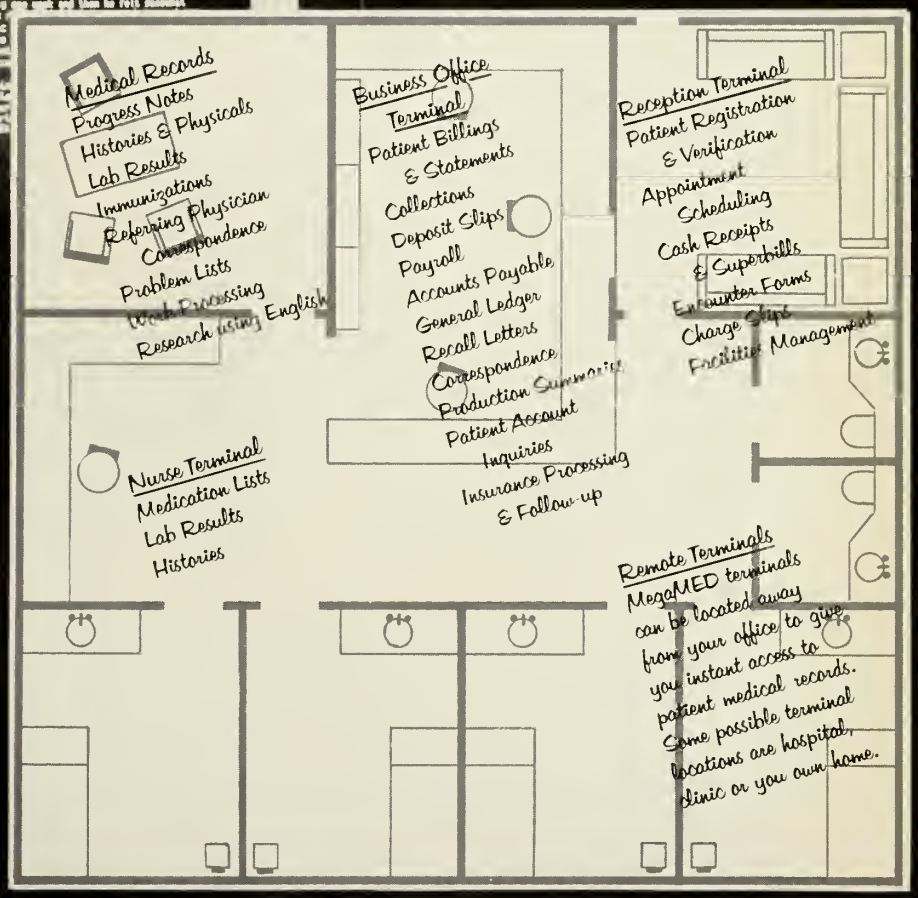
June 29-30—**Genetics in Modern Obstetrics—Advances in Prenatal Diagnosis.** Santa Fe. Friday-Saturday. Hilton Inn. 10 hrs. NM Cat. IV. Contact: VIVIGEN, Sterling Puck, MD, 550 St. Michaels Drive, Santa Fe 87501. (505) 988-9744.

July 12-14—**New Mexico Ophthalmological Society Annual Meeting.** Santa Fe. Thursday-Saturday. Hilton Inn. 8½ hrs. NM Cat. IV,

(Continued on Page 998)

MegaMED is more than just a front office computer!

MegaMED is an established medical office computer management system that doesn't stop at keeping accounts and preparing statements. Physicians throughout the country use MegaMED to handle appointment scheduling, prepare patient encounter forms, develop production summaries, keep detailed patient medical records, and much more. We hope this advertisement helps you analyze your needs in a medical office management system.



One of the features of MegaMED with which we are particularly pleased is it's ability to keep and search patient medical records in plain English. You can enter progress notes, medications, etc., just as you would write them on a chart. And later, you can direct MegaMED to search those records for specific information.

Example: A list of all female patients over the age of 50 who have taken a specific medication in the last 15 months.

Since you speak English, we thought your computer should understand it.

After reviewing the functions performed by MegaMED in this medical office, we imagine you will want to know more about what it can do in your medical office. We will be glad to help you discover that – call us at 801-486-5359 – or write us at 140 West 2100 South, Salt Lake City, Utah 84115.

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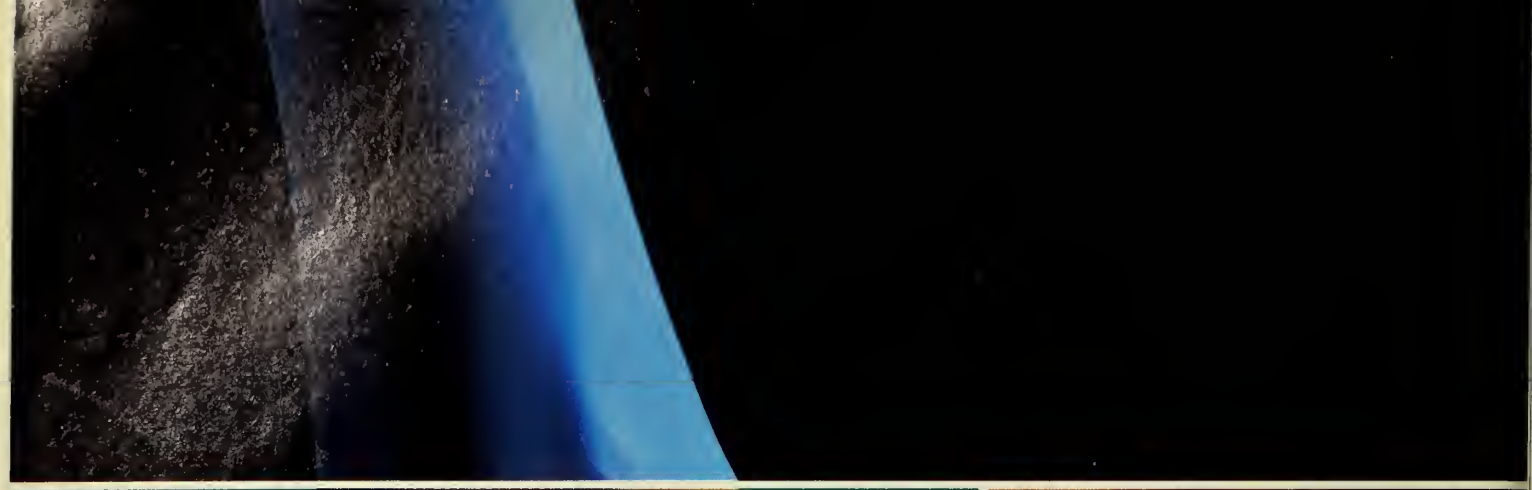

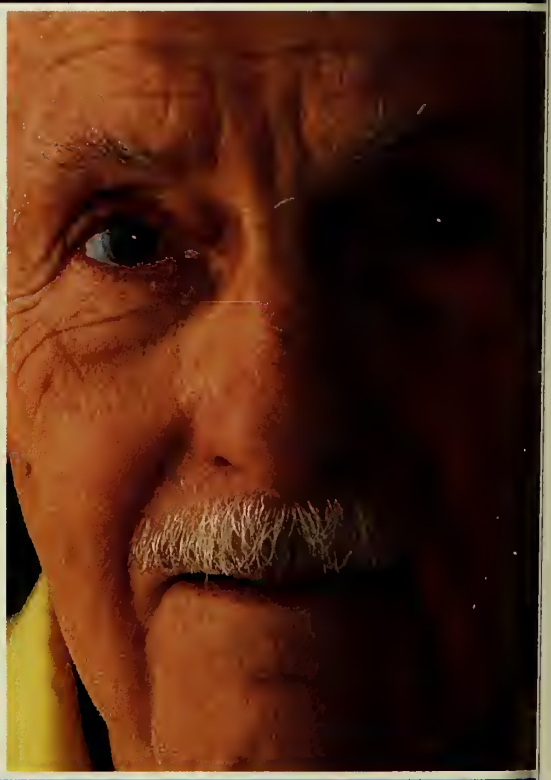

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(ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

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Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.
Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.
Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.
The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.
Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.
Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.
Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.
Incidence Greater than 1% (but less than 3%)–Probable Causal Relationship
Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).
Incidence less than 1%–Probable Causal Relationship*
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence less than 1%–Causal Relationship Unknown*
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.
*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
Caution: Federal law prohibits dispensing without prescription.

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Upjohn

(Continued from Page 994)

AMA Cat. I. Contact: Kim Knowles, MD, 1452 St. Francis Drive, Santa Fe 87501. (505) 982-2509.

July 16-19—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 26-28—**General Surgical Update 1984.** Albuquerque. Thursday-Saturday. Marriott Hotel. 15 hrs. AMA Cat. I, NM Cat. IV. Contact: UNM School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

November 9-10—**New Mexico Medical Society Interim Meeting—Sports Medicine.** Clovis. Friday-Saturday. 8 hrs. AMA Cat. I, NM Cat. IV. Contact: NMMS, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * *

EMERGENCY MEDICINE

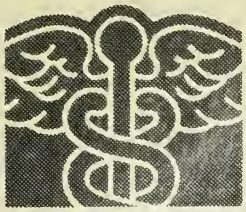
November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

SURGERY

July 8-11—**Practical Plastic Surgery for the Primary Care Physician.** Bend. Monday-Wednesday. Sunriver Resort. Contact: OHSU-CME.



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- Call Bob Tarbell or Sula Brown at (714) 870-1100 - La Habra
- Call Saburo Tachibana at (415) 788-3600 - San Francisco

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November 30-December 1—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

June 22-23—**Exercise and Fitness.** Portland. Friday-Saturday. Red Lion-Lincoln Street. Contact: OHSU-CME.

September 7-8—**The Ashland Conference: Immunology and Allergy in Primary Care.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7:00 a.m. to 9:00 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE GRAND ROUNDS

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Wednesday—8:00 a.m. to 9:00 a.m. Contact: Thomas Schwenk, MD, (801) 581-8633.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8:00 a.m. to 9:00 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8:00 a.m. to 9:00 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30 a.m. to 8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext. 2143).

* * *

June 18-21—**School on Alcoholism and Other Drug Dependencies** (Sponsor: University of Utah). Monday-Thursday. University Medical Center. 26 hrs. $300. Contact: James Swenson, MD, (801) 581-7985.

July 15-20—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, Wyoming. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art** (Sponsor: University of Utah). Wednesday. Jackson Lake Lodge, Wyoming. Contact: John D. Armstrong, MD, (801) 581-7553.

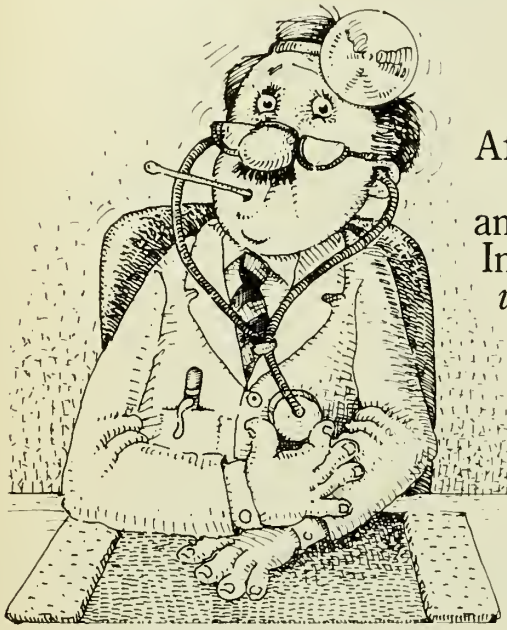
Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

(Continued on Page 1010)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

Your practice very best



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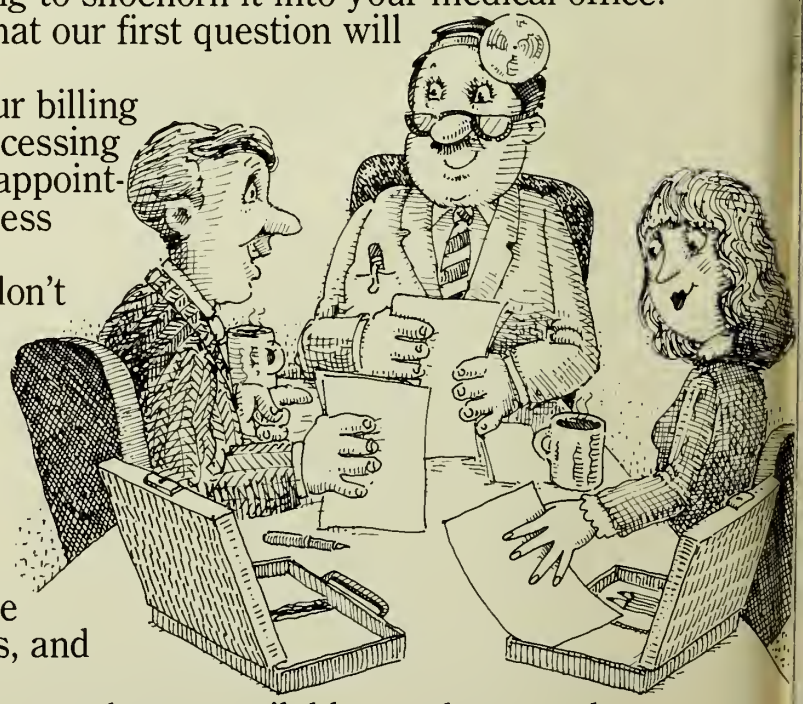
Phone or write Management Systems of Wausau and discover how smoothly your practice can run. Imagine your bills going out on time *without any worry or bother on your part at all.* Imagine insurance claims processed without problems, recall notices for follow-up care issued automatically, lists of patients and surgeries provided on demand.

Please be assured that we won't introduce new medical management procedures and then bid you a fast farewell. We've built a reputation for outstanding service; we'll always be there to help. Our method is to diagnose your problems and then offer consultations, prescriptions and continual support to solve them.

DIAGNOSES Unlike typical computer management companies, we never start by presenting a service and trying to shoehorn it into your medical office. Actually, we offer so many services that our first question will be: "What do you really need?"

Then let's sit down and list your billing needs, collection needs, insurance processing needs, management reporting needs, appointment scheduling needs, general business needs, and medical reporting needs. Together, we'll also clarify what you don't need. Only then can an efficient, cost-effective program be chosen for your medical office.

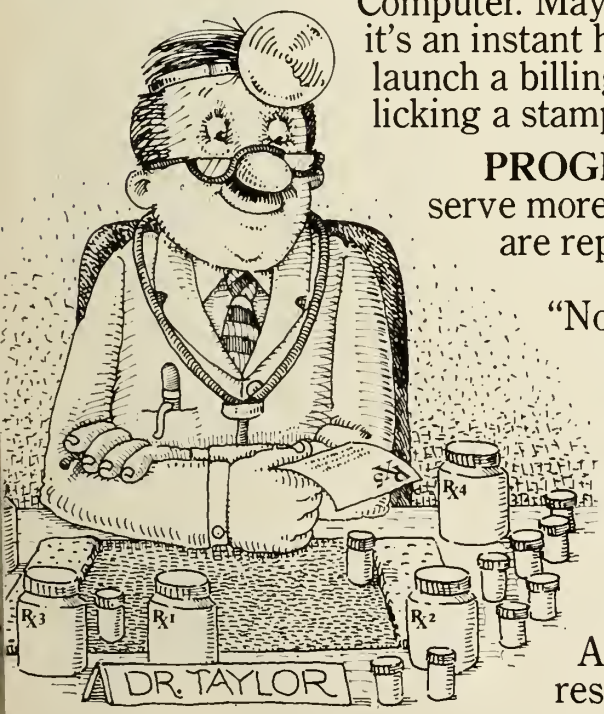


CONSULTATIONS In plain English, not computer or management jargon, we'll explain how to strengthen your financial control. For example, we can help you design more effective statements, collection notices, and routing slips.

Please remember that, while we are always available, we do not make excessive demands on your time. The idea is not to take time, but to save time. Our goal is to free your staff to devote more time to patients and less to paperwork.

deserves the of care.

PRESCRIPTIONS We prescribe only what you really need. Maybe it's a service bureau relationship to get your bills out. Maybe it's your own IBM Personal Computer. Maybe it's a sophisticated in-house system. Maybe it's an instant hook up with computers at Wausau that lets you launch a billing cycle without addressing an envelope or licking a stamp.



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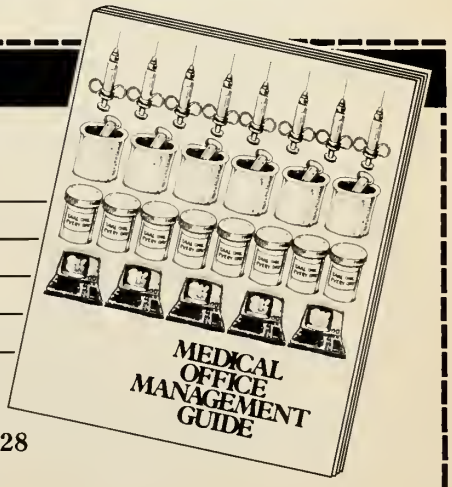

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PHYSICIANS WANTED

GENERAL INTERNIST, Board certified/eligible: Multi-specialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact A. J. Grose, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

BEAUTIFUL WASHINGTON STATE—One General Internist sought to join another Internist in an HMO with 15 well-trained Board-certified Family Practitioners in Spokane, Washington. An unusual opportunity to serve as a full-time in-house consultant in an organization where continuity of care, patient education/preventive medicine, and high quality personal-style care are emphasized. Prefer interest/training in medical Oncology or Geriatrics. Excellent salary and benefits. Spokane is a delightful city containing an exceptionally fine medical community and superb, year-round outdoor recreation. Affiliated with Group Health Cooperative of Puget Sound. For further information contact: Carl Baum, MD, Group Health of Spokane, N. 3919 Maple Street, Spokane, WA 99205; (509) 326-6900.

PEDIATRICIAN—Solo practice in Southeastern New Mexico. Ideal family living in prosperous community serving 85,000. Income guarantee, new office available adjacent to 106-bed JCAH-accredited hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

NEUROSURGEON—Southeastern New Mexico. To establish new practice in growing community serving 85,000. New 106-bed hospital, JCAH-accredited. Has newly operational CAT. Income guarantee. New office available adjacent to hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

ORTHOPEDIC SURGEON—Solo practice in Southwestern New Mexico. Ideal family living in prosperous community serving 85,000. Income guarantee. New office located adjacent to 106-bed, JCAH-accredited hospital. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

OBSTETRICIAN GYNECOLOGIST—Board certified or eligible—to join multispecialty group. Hospital facilities adjacent. Gateway to San Juan Islands. Excellent recreational opportunities. Send CV to: Dr Harold Clure, Family and Internal Medicine Associates, 24th & M Avenue, Anacortes, WA 98221, or call (206) 293-3101.

PHYSICIANS WANTED

BOARD CERTIFIED OR ELIGIBLE INTERNIST to become associated with two established physicians in primary care practice in Southern California. Practice incorporated with established pension, continuing education and life insurance programs. Competitive starting compensation with full participation in earnings as ultimate objective. California license required. This opportunity could be of interest to Board certified or eligible Hematologist/Oncologist as an avenue to establish a practice in his specialty. Reply: Medical Practice, P.O. Box 6504, Fullerton, CA 92634-6504.

OREGON—GENERAL INTERNIST sought for multiplespecialty group. Beautiful rural community, 38 miles from Portland. Send CV to Adm., 420 E. 5th St, McMinnville, OR 97128; phone to staff member (503) 472-6161.

CLINIC PHYSICIAN—Rural Primary Health Care Outpatient Center is seeking Clinic Physician for provision of outpatient clinical services in a multi-cultural rural wilderness setting. Contact: Ramah Navajo School Board, Inc., Personnel Department, P.O. Drawer A, Pine Hill, NM 87321.

ENDOCRINOLOGIST: Immediate opening in private practice. Exclusively subspecialty: Endo/Diabetes. Los Angeles. Reply with CV to Box 6421, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PHYSICIANS WANTED

CLINICAL FACULTY, FAMILY PRACTICE—Board certified Family Physician needed to staff FP residency satellite office in a community of 3,500 population located 15 mi. from the primary office in Spokane, Washington. Duties include: full spectrum of patient care (including OB), responsibility for satellite office management, and supervision/teaching of FP residents while working in the satellite. Univ. of Washington clinical faculty appointment. Salary based on experience, excellent fringe benefits. Send inquiries with CV to: Kenneth E. Gudgel, MD, Director, Family Medicine Spokane, South 511 Pine St, Spokane, WA 99202.

EXCELLENT OPPORTUNITY FOR BOARD CERTIFIED INTERNIST. Position available imediately in well-established practice—owner retiring. Flexible arrangements. Beautiful recreation area. CV with reply to: Welty & Welty, W. 407 Riverside, #1680, Spokane, WA 99201.

INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career-oriented emergency physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 234-4795, or send CV to EMP, P.C., P.O. Box 3398, Casper, WY 82602-3398.

SOUTH DAKOTA: Expanding physician-owned emergency group has opening for full-time career-oriented emergency physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD., (307) 234-4795, or send CV to EMP, P.C., P.O. Box 3398, Casper, WY 82602-3398.

WANTED FAMILY PRACTITIONER(S). Gateway to the Oregon Caves. 15,000 plus residents In lovely valley. Excellent referral system. 29 miles from hospitals Enjoy the excitement of a rural family practice and time to spend outdoors. Board of Directors anxious to expand to meet community needs. Now available, one-half fully equipped modern clinic. Room for one or two physicians with excellent expansion potential. Expansion could be emergency type care or convalescent home. Call AC (503) 592-3916 or 592-2224 evenings or weekends.

ER PHYSICIAN needed for emergency departmen in small community hospital located on the coast 25 miles south of San Francisco. Reply: Dr Timothy Whelan, St. Catherine's Hospital, Moss Beach, CA 94038.

(Continued on Page 1006)

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Phone _____ Prior Service? Yes ____ No ____

Medical Specialty _____ Date of Birth _____

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(Continued from Page 1004)

CARDIOLOGIST: Invasive or non-invasive. Preferably speaks some Spanish. An opportunity to develop testing in a small community hospital and a private practice in California's Imperial Valley. Financial arrangements negotiable (rent subsidy, etc). Reply to Box 6432, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

THE OFFICE OF WORKERS' COMPENSATION PROGRAMS is seeking Board eligible/certified physicians to provide second opinion evaluations. Specialties include Orthopedics, ENT, Psychiatry, Cardiology, and Neurosurgery/Neurology. Locations include the San Francisco Bay Area, the Greater Los Angeles Area, San Diego, and Las Vegas. A contracted second opinion physician is precluded from also providing referee exams and is subject to fee schedule. Please send curriculum vitae to: Gerald T. Cullen, Contracting Officer, Office of Workers' Compensation Programs, US Dept. of Labor, 450 Golden Gate Ave., P.O. Box 36066, San Francisco, CA 94102.

HEALTH OFFICER—Natrona County Board of Health invites applications for County Health Officer. Required MD, eligibility for licensure in Wyoming, MPH degree or five years experience as a paid physician in preventive medicine and environmental health. 70,000 population located in the heart of prime hunting and fishing. Salary $50,000 to $65,000 depending on qualifications and experience. Excellent fringe benefits. Send curriculum vitae by September 1, 1984, to Search Committee, Health Department, 1200 E. 3rd, Casper, WY 82601. EOE

PHYSICIAN FOR PLASMAPHORESIS CENTER, needed to start mid-June. California license req., 4 days per week, no call, low stress position with time for personal reading. North San Francisco Bay City. Contact: Jerome Murphy, MD, c/o Plasma Resources, 332 Tennessee Street, Vallejo, CA 94590. Ph: (707) 644-4119.

CALIFORNIA—URGENT CARE. Positions available for Summer 1984 in free-standing, urgent care settings in several locations. Board certification or eligibility in emergency medicine, family practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Avenue, Suite 500, Oakland, CA 94610, (415) 832-6400.

PHYSICIAN FOR INITIAL CARE SECTION of Wenatchee Valley Clinic. Salary with fringe benefits. 46 hours/week. Acute Medical/Pediatric mix in large multispecialty clinic situated in lovely north central Washington. Outdoor recreation in abundance, on 'dry side' of Cascade Mountains. Superb family community. Reply with CV to John Crewes, MD, PO Box 489, Wenatchee, WA 98801; (509) 663-8711.

PHYSICIANS: URGENT CARE: Rapidly expanding medical group servicing Urgent Care Network throughout California (San Diego, Orange County, Bay Areas, and Sacramento) needs Independent Contractors with Primary Care, ER, Occupational Medicine Specialities. California licenses required; prior outpatient practice a plus. Client provides all personnel facilities, ancillary equipment with Group providing malpractice. Guaranteed minimum plus monthly incentive, stock options available. No relocation assistance. Contact Personnel Urgent Care Centers of America, Inc., 2737 Walsh Avenue, Santa Clara, CA 95051; (408) 727-1900. EOE

POSITION AVAILABLE IN GENERAL INTERNAL MEDICINE. Community offers ideal family living in town of 12,000 people, liberal fringe benefits—life insurance, health insurance, 30 days vacation plus 15 days sick leave each year. Complete malpractice insurance coverage provided. An unexcelled opportunity to engage in a challenging medical practice in a rural setting offering unlimited recreational opportunities—hunting, fishing, skiing, plus fresh, clean air in abundance. Contact: P. J. Shannon, Chief, Personnel Service, VA Medical Center, Miles City, MT 59301. Telephone: (406) 232-3060 Ext. 201.

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Challenging opportunity to provide preventative care including physical examinations, clinical duties, emergency treatment, consulting to management regarding the health and safety of employees, maintaining effective records for the medical data base and assisting the medical director with special projects.

Requirements: Certification in occupational medicine or a related specialty and experience in an industrial occupational health program. Sensitive to issues of women and all other segments of the work force; able to be a role model for physical fitness and optimal health programs; eligible for DOE security clearance.

Call **George M. Lawton, M.D., at (415) 422-7459** or send your resume to: **Muriel Bauer, Lawrence Livermore National Laboratory, P.O. Box 5510, Dept. KWA-614, Livermore, California 94550.**

An equal opportunity employer m/f/h/v.
U.S. citizenship is required.

University of California
Lawrence Livermore National Laboratory

DERMATOLOGIST WANTED. Southern California. Board certified or eligible for permanent part-time two to three days weekly. Salary negotiable. Reply with CV to Box 6429, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

SOUTHERN CALIFORNIA—Full-time position in busy urgicenter for experienced physician. Pleasant personality a must. Career opportunity for right person. Send CV to EMGT, 19000 Hawthorne Blvd., Torrance, CA 90503; (213) 542-6982.

SAN FRANCISCO and SEATTLE: CHEC Medical Centers has practice opportunities for physicians interested in Primary Medicine/minor Emergency Care. Guaranteed base plus financial incentives, malpractice coverage, health insurance, paid vacation and CME time, and practice equity provided. Please send CV to Richard Miller, Director of Physician Services, CHEC Medical Centers, 2200 Sixth Avenue, Suite 1200-BB, Seattle, WA 98121.

GENERAL/FAMILY PRACTICE

CIGNA Healthplans of California is offering a career opportunity to General and Family Practitioners with acute and preventive medicine orientation. Our HMO provides a personal patient population and a continuity of care as well as an excellent compensation package. Send curriculum vitae to:

Director Physician Recruitment
CIGNA Healthplans of California
700 N. Brand Blvd, Ste. 500
Glendale, CA 91203

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GENERAL SURGEON, Board certified/eligible: multispecialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact J. W. Devney, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

CARDIOLOGIST WANTED, Board certified or Board eligible invasive, non-invasive Cardiologist to join our group in July, 1984. The Inland Cardiovascular Medical Group is located in Orange and Riverside counties in Southern California. We are offering a competitive salary and a fringe benefit package leading to a partnership. Please send the necessary references and CV to John R. Gehrum, Administrator, Inland Cardiovascular Medical Group, 770 Magnolia Suite 2 A and B, Corona, CA 91720.

THE WALLA WALLA CLINIC is accepting applications from Family Practitioners for its rural satellite locations. Satellites are approximately 15 miles from the Clinic in towns of 6,000 population. One position is an addition to an established practice. The Clinic is a 26 physician multispecialty health care provider located in Southeastern Washington. The population of our service area is approximately 100,000. The Walla Walla Community is a college town of 30,000, and the primary industrial base is agriculture. Walla Walla is nestled in the foothills of the Blue Mountains with limitless recreational opportunities. Please submit your CV to the Search Committee, Walla Walla Clinic, 55 West Tietan, Walla Walla, WA 99362; (509) 525-3720.

INTERNIST, CALIFORNIA, two American trained, Board certified General Internists seek the same for association in busy practice in Central San Joaquin Valley city of 50,000. No investment required. Subspecialist with interest in doing some general Internal Medicine desirable. Excellent recreational area with access to San Francisco, Yosemite and coast. Opportunity to establish a busy independent practice with no initial investment. Reply to: Box 6434, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

THE DEPARTMENT OF FAMILY MEDICINE at University of California, Irvine is recruiting for a Spanish-speaking Pediatrician with MPH degree and teaching experience. The appointment will be at the assistant professor level in the clinical series. Send curriculum vitae to: J. Dennis Mull, MD, Chairman, Department of Family Medicine, University of California, Irvine, 101 City Drive South, Orange, CA 92668. An Affirmative Action/Equal Opportunity Employer.

GENERAL PRACTITIONERS—Specialists—Full-time positions or Locum Tenens. If you're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

BOARD CERTIFIED Oncologist, Cardiologist, Internist, Neurosurgeon, Otorhinolaryngologist for Southeastern Washington—Tri-Cities, 150,000 population. Outdoor activities abound. Group or solo opportunities. Contact Vesta Skiens, Kennewick General Hospital (509) 586-6111 (309).

F/T OB/GYN for growing multispecialty group in sunny L.A. Spanish very important. 1st year compensation negotiable. Partnership potential 2nd year. CV to Med. Dir. Box 6435, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTITIONER, BC/BE for challenging work with Community Clinic. 3 days per week plus call, OB included. Benefits. Send CV to Betty Arterberry, Personnel Officer, Sonoma County Indian Health Project, Inc., 2240 Professional Drive, Santa Rosa, CA 95401.

PLASTIC SURGEON and GENERAL SURGEON. Surgical center office and facilities available. Very reasonable terms with excellent possibilities. Contact Administrator, San Fernando Surgical Center, 1056 No. Maclay, San Fernando, CA 91340; Tel: (818) 365-0671.

(Continued on Page 1012)

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In clinical anxiety,

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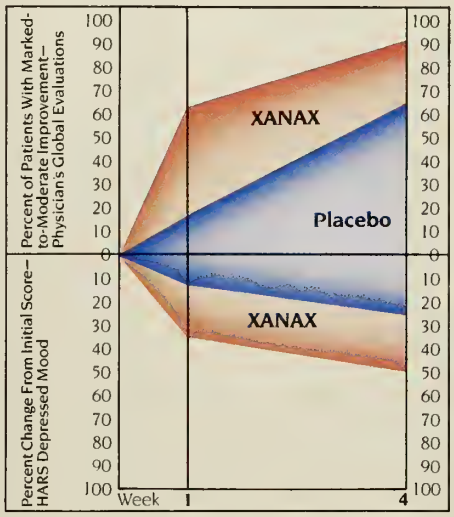
depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

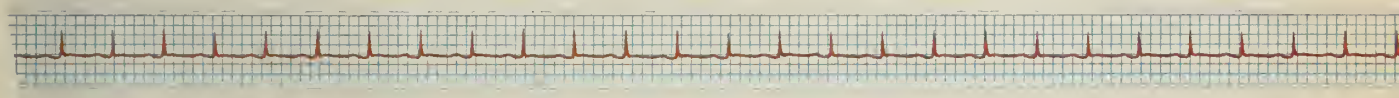
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy



- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file, The Upjohn Company.
Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets
alprazolam Ⓒ IV

XANAX® Tablets
(alprazolam) ©

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about, (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

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CONTINUING MEDICAL EDUCATION

(Continued from Page 1001)

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 15—**Medical Problems of the Abdomen.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15-16—**Imaging Techniques and Computers in Radiation Therapy.** Seattle. Friday-Saturday. Sheraton. Contact: U/W.

June 15-17—**Nutrition Update for Clinical Dieticians.** Union. Friday-Sunday. Alderbrook Inn. Contact: U/W.

June 19-20—**Pathobiology Immune Glomerular Disease.** Seattle. Tuesday-Wednesday. Kane Hall. Contact: U/W.

June 21-22—**Stroke: Current Concept.** Seattle. Thursday-Friday. 8:30 a.m. to 5:00 p.m. Gould Auditorium. $150, physicians; $75, others. 12 hrs. Cat. I. Contact: Charlotte Kennedy, Northwest Hospital, 1550 N. 115th, Seattle 98133. (206) 364-0500, Ext. 1737.

June 22—**New Pneumonias.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 23-27—(IDAHO) **Ethics at the Edges of Life.** Sun Valley. Saturday-Wednesday. Elkhorn. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, PO Box 900, Seattle, WA 98101. (206) 223-6898.

June 29—**Sinusitis.** Seattle. Friday. Riverton Hospital. Contact: U/W.

July 4-10—(OREGON) **Medicine and Civilization.** Bend. Wednesday-Tuesday. Inn of the 7th Mountain. Contact: U/W.

July 10-13—(OREGON) **Medicine in Shakespeare's Time.** Ashland. Tuesday-Friday. Contact: U/W.

July 11-13—**Second Annual Conference on Occupational Hazards to Health Care Workers.** Seattle. Wednesday-Friday. Contact: Northwest Center for Occupational Health and Safety. Department of Environmental Health, SC-34, University of Washington, Seattle 98195. (206) 543-1069.

July 22-26—**Annual Summer Meeting 1984. Washington State Academy of Ophthalmology.** Orcas Island. Sunday-Thursday. Rosario Resort. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

July 27-29—**Seafair VI Pediatric Anesthesia and Intensive Care.** Seattle. Friday-Sunday. Seattle Sheraton. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave, Suite 900, Seattle 98121. (206) 623-4801.

August 17-23—(OREGON) **Psychiatry for Primary Physicians.** Friday-Thursday. Sunriver Resort, Sunriver. Contact: U/W.

August 29-September 4—(ALBERTA) **Scientific Aspects of the Art of Dance.** Banff Centre, Banff, Alberta. Contact: U/W.

September 5-7—**Recent Advances in Obesity.** Seattle. Wednesday-Friday. Health Sciences Center. Contact: U/W.

September 6-7—**Symposium on Breast Disease.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

September 7-8—**Nutrition and Bone Metabolism.** Seattle. Friday-Saturday. Health Sciences Center. Contact: U/W.

September 8-15—(ALBERTA) **Neurosurgery of Pain.** Banff. Saturday-Saturday. Banff Park Lodge. Contact: U/W.

September 10-14—**Advances in Family Practice.** Seattle. Monday-Friday. Health Sciences Center. Contact: U/W.

September 10-14—**Advances in Family Practice ACLS.** Seattle. Monday-Friday. Health Sciences Center. Contact: U/W.

September 12-14—**Dermatologic Therapeutic Hotline.** Orcas Island. Wednesday-Friday. Rosario Resort. Contact: Paul H. Jacobs, MD, Department of Dermatology, Stanford University Medical Center, Stanford, CA 94305. (415) 497-7854.

September 26—**Advances in Lab Medicine.** Seattle. Wednesday. Health Sciences Center. Contact: U/W.

WYOMING

June 24-28—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Thursday. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 634-2424.

July 4-6—**Stress and the Heart: Diagnosis, Prevention Management and Rehabilitation.** American College of Cardiology and the Heart-Lung Center of St. Luke's Hospital of Phoenix at Jackson Lake Lodge, Moran. 13 hrs. $240, ACC members; $295, nonmembers. Contact: ACC, Extramural Programs Dept., 9111 Old Georgetown Rd., Bethesda, MD 20814. (301) 897-5400.

July 15-20—**Summer Update in Clinical Microbiology and Immunology.** University of Utah at Jackson Hole. Sunday-Friday. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art.** University of Utah at Jackson Lake Lodge. Wednesday. Contact: John D. Armstrong, MD, (801) 581-7553.

September 9-15—**Effective Management of Common Sports Injuries: An EPIC Medical Expedition.** Bicycle touring through Yellowstone and Grand Teton National Parks. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

(Continued from Page 1006)

PHYSICIAN WANTED

SAN FRANCISCO (2) OPPORTUNITIES: 1/FP needed with basic GYN, minor surgery and Obstetrics experience. 1/LR physician with experience in minor surgery, basic Orthopedics end Internal Medicine. Positions available beginning summer 1984. Group-solo practice. CV to: Box 6433, The Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

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CARDIOLOGIST, 38, Board certified, currently working with large internal medical group in California; wishes to locate in California with Cardiologist(s) or Internist with heavy cardiologist practice. Skilled in CCU-ICU care, pacemakers, consultation, non-invasive techniques. Reply Box 6431, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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INTERNAL MEDICINE PRACTICE—One hour North of S.F. Must sell immediately to begin ER position July 1984. Very desirable practice for suitable IM or FP physician. Call evenings: (707) 823-4237.

UNIQUE OPPORTUNITY for phased purchase of active internal medicine practice, Napa Valley, California. Excellent office and hospital facilities. Sub-specialty training in Nephrology or Oncology helpful. CV required. Box 6426, Western Journal of Medicine, 44 Gough St., San Francisco, 94103.

FAMILY PRACTICE IN IDAHO: Two-doctor clinic located in Kamiah. Practice is managed by a neighboring Hospital which pays all expenses. Salary based on % of gross revenue with minimum guarantee. Kamiah is located on the Clearwater River and is adjacent to the River of No Return and Selway-Bitterroot Wilderness Areas. This practice is a gold mine. Contact John Hull, Administrator, St Mary's Hospital, Cottonwood, ID 83522; (208) 962-3251.

SOUTHERN CALIFORNIA FAMILY MEDICAL PRACTICE FOR SALE. Idyllic location near ocean in beautiful Santa Barbara. Gross $150,000. Physician owner must leave country for family reasons. Call (805) 967-9668.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

NEUROLOGIC EMERGENCIES—Edited by Michael P. Earnest, MD, Associate Professor of Neurology and Preventive Medicine, University of Colorado Health Sciences Center, and Director, Department of Neurology, Denver General Hospital. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 516 pages, $55.00.

NEUROLOGY FOR NON-NEUROLOGISTS—Edited by Wigbert C. Wiederholt, MD, Department of Neurosciences, School of Medicine, University of California, San Diego, La Jolla, Calif. Academic Press, Inc., 111 Fifth Ave., New York, NY 10003, 1982. 400 pages, $37.50.

NEUROPEPTIDES: BASIC AND CLINICAL ASPECTS—PROCEEDINGS OF THE ELEVENTH PFIZER INTERNATIONAL SYMPOSIUM, SEPTEMBER 1981—Edited by George Fink, MD, MA, DPhil, Director of the MRC Brain Metabolism Unit, University Department of Pharmacology and The Thomas Clouston Clinic, Royal Edinburgh Hospital, Edinburgh; and Lawrence J. Whalley, MD, MRCPsych, Clinical Scientist, MRC Brain Metabolism Unit, Edinburgh, and Honorary Consultant Psychiatrist, The Thomas Clouston Clinic, Royal Edinburgh Hospital, Edinburgh. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 277 pages, $59.00.

NMR: A PRIMER FOR MEDICAL IMAGING—Gerald L. Wolf, PhD, MD, Associate Chief of Staff/Research, VA Medical Center, Philadelphia, Professor, Departments of Radiology and Pharmacology, University of Pennsylvania, Philadelphia; and Carol Popp, MD, PhD, Department of Radiology, University of Pennsylvania, Resident, Graduate Hospital, Philadelphia. Slack Incorporated, 6900 Grove Road, Thorofare, NJ 08086, 1984. 86 pages, $19.50 (paperback).

NOW THAT YOU'VE INCORPORATED: Coping with Changing Tax Laws—4th Edition—Sheldon H. Gorlick, JD, Medical Economics Books, 680 Kinderkamack Road, Oradell, NJ 07649, 1983. 152 pages, $22.95.

NUTRITION AND HEART DISEASE—Vol. 6 in Contemporary Issues in Clinical Nutrition—Edited by Elaine B. Feldman, MD, Professor of Medicine; Chief, Section of Nutrition, and Director, Clinical Nutrition Research Unit and Georgia Institute of Human Nutrition, Medical College of Georgia, Augusta. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 211 pages, $35.00.

NUTRITION IN HEMATOLOGY—Volume 5 in Contemporary Issues in Clinical Nutrition—Edited by John Lindenbaum, MD, Professor of Medicine, Columbia University College of Physicians and Surgeons, and Associate Director, Medical Service, Harlem Hospital Center, New York. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 320 pages, $37.50.

THE OFFICIAL M. D. HANDBOOK—Anne Eva Ricks, MD. The New American Library, Inc., 1633 Broadway, New York, NY 10019, 1983. 161 pages, $4.95 (paperback).

OTC HANDBOOK: WHAT TO RECOMMEND & WHY—Second Edition—Richard Harkness, RPh. Medical Economics Books, Oradell, NJ 07649, 1983. 204 pages, $12.95 (softbound).

AN OUTLINE OF CLINICAL DIAGNOSIS—Brian J. Prout, PhD, FRCP (Lond), Consultant Physician, Royal Cornwall Hospital (Treliske), Truro, Cornwall, England, and John G. Cooper, BSc, MB, MRCP (Lond), Assistant Physician, Hamer Hospital, Sykehus, Norway. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 255 pages, $19.50 (softbound).

OUTLINE OF FRACTURES—INCLUDING JOINT INJURIES—Eighth Edition—John Crawford Adams, MD(London), MS(London), FRCS(England), Honorary Consulting Orthopaedic Surgeon, St. Mary's Hospital, London, and Civil Consultant in Orthopaedic Surgery, Royal Air Force. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 314 pages, $12.50 (paperback).

OVARIAN MALIGNANCIES: The Clinical Care of Adults and Adolescents, Volume 4 in the Current Reviews in Obstetrics & Gynaecology series—M. Steven Piver, MD, Deputy Chief (Gynecology), Clinical Professor, Department of Gynecologic Oncology, Roswell Park Memorial Institute, Buffalo. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 200 pages, $19.50 (softbound).

PATHOLOGY OF GLOMERULAR DISEASE: Volume I in Contemporary Issues in Surgical Pathology Series—Edited by Seymour Rosen, MD, Director of Surgical Pathology, Beth Israel Hospital, and Associate Professor of Pathology, Harvard Medical School, Boston. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 268 pages, $45.00.

PATHOLOGY OF THE COLON, SMALL INTESTINE, AND ANUS—Vol. 2 in Contemporary Issues in Surgical Pathology—Edited by H. Thomas Norris, MD, Professor and Chairman, Department of Clinical Pathology and Diagnostic Medicine, East Carolina University School of Medicine, and Chief of Pathology, Pitt County Memorial Hospital, Greenville, North Carolina. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 327 pages, $50.00.

PEDIATRIC EPILEPTOLOGY—CLASSIFICATION AND MANAGEMENT OF SEIZURES IN CHILDREN—Fritz E. Dreifuss, MB, FRCP, FRACP, Professor of Neurology, School of Medicine, University of Virginia, and Director, Comprehensive Epilepsy Program, Charlottesville. John Wright • PSG, Inc., 545 Great Rd., Littleton, MA 01460, 1983. 295 pages, $35.00.

PHYSICAL DIAGNOSIS—MEDICAL EXAMINATION REVIEW—Second Edition—John H. Holbrook, MD, Associate Professor of Internal Medicine, University of Utah School of Medicine, Salt Lake City. Medical Examination Publishing Co., Inc., 969 Stewart Ave., Garden City, NY 11530, 1983. 199 pages, $12.75 (softbound).

POSTGRADUATE TEXTBOOK OF CLINICAL ORTHOPAEDICS—Edited by Nigel H. Harris, MA, FRCS, Consultant Orthopaedic Surgeon, St Mary's Hospital, London. John Wright • PSG Inc., 545 Great Rd, Littleton, MA 01460, 1983. 1,010 pages, $120.00.

PRACTICAL RHEUMATOLOGY—Edited by Timothy M. Spiegel, MD, Assistant Professor of Medicine, Division of Rheumatology, UCLA School of Medicine, Los Angeles. John Wiley & Sons, Inc., One Wiley Dr., Somerset, NJ 08873, 1983. 375 pages, $29.95.

THE PREMATURE BABY BOOK: A Parents' Guide to Coping and Caring in the First Years—Helen Harrison with Ann Kositsky, RN. St. Martin's Press, 175 Fifth Avenue, New York, NY 10010, 1983. 273 pages, $15.95 (softbound).

PRIMARY CARE GERIATRICS—A CASE-BASED LEARNING PROGRAM—Richard J. Ham, MD, Joseph M. Holtzman, PhD, Michelle L. Marcy, MS, and Marcia R. Smith, PhD; prepared under the auspices of the American Geriatrics Society. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 311 pages, $39.50 (softbound).

PROGRESS IN MEDICAL GENETICS—Volume V—Genetics of Cardiovascular Disease—Edited by Arthur G. Steinberg, PhD, Francis Hobart Herrick Professor Emeritus of Biology, Department of Biology, and Professor of Human Genetics, Case Western Reserve University, Cleveland; Alexander G. Bearn, MD, Senior Vice President, Medical and Scientific Affairs, Merck Sharp & Dohme International, Rahway, New Jersey, and Professor of Medicine, Cornell University Medical Center, New York; Arno G. Motulsky, MD, Professor of Medicine and Genetics and Director, Center for Inherited Diseases, University of Washington, Seattle; and Barton Childs, MD, Professor Emeritus of Pediatrics, The Johns Hopkins University, Baltimore. W. B. Saunders Company, West Washington Square, Philadelphia, PA 19105, 1983. 402 pages, $60.00.

PROGRESSIVE EXERCISE THERAPY IN REHABILITATION AND PHYSICAL EDUCATION—Fourth Edition—John H. C. Colson, FCSP, FSRG, DipTRG, DipCOT, Remedial Therapy Representative, NHS Health Advisory Service, and Frank W. Collison, MSRG, Head Remedial Gymnast, and Clinical Supervisor, Rehabilitation Department, Pinderfields General Hospital. John Wright • PSG, Inc., 545 Great Rd., Littleton, MA 01460, 1983 278 pages, $17.50 (softbound).

PSORIASIS: CELL PROLIFERATION—Edited by N. A. Wright, MA, MD, PhD, MRCPath, Professor and Director, Department of Histopathology, Royal Postgraduate Medical School, and R. S. Samplejohn, PhD, The Richard Dimbleby Cancer Research Department, St Thomas' Hospital Medical School, London. Churchill Livingstone Inc., 1560 Broadway, NY 10036, 1983. 404 pages, $65.00.

PSYCHODYNAMIC PERSPECTIVES ON RELIGION, SECT AND CULT—Edited by David A. Halperin, MD, Assistant Clinical Professor of Psychiatry, Mount Sinai School of Medicine of the City University of New York, and Consulting Psychiatrist, Cult Hotline and Treatment Program of Jewish Board of Family and Children's Services, and Cult Information and Treatment Program of Westchester Jewish Community Services, New York. John Wright • PSG Inc., 545 Great Rd., Littleton, MA 01460, 1983. 382 pages, $44.50.

RADIOGRAPHIC TECHNIQUES RELATED TO PATHOLOGY—Third Edition—Margaret A. Clifford, DCR, Radiographer, Lord Mayor Treloers Hospital, Alton, Hants, and Ann E. Drummond, BA, FCR, District Superintendent Radiographer, Frimley Park Hospital, Frimley, Surrey, England. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 85 pages, $8.50 (softbound).

RECENT ADVANCES IN CLINICAL IMMUNOLOGY—No. 3—Edited by R. A. Thompson, MBE, BSc, MBBS, FRCP, FRCPath, Consultant Immunologist and Director, Regional Department of Immunology, East Birmingham Hospital, Birmingham, United Kingdom, and Noel R. Rose, MD, PhD, Professor and Chairman, Department of Immunology and Infectious Diseases, The Johns Hopkins University, Baltimore. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 308 pages, $60.00.

RECENT ADVANCES IN CLINICAL VIROLOGY—No. 3—Edited by A. P. Waterson, MD(Cantab), FRCP(Lond), FRCPath, Emeritus Professor of Virology, University of London, and Consultant Virologist, Hammersmith Hospital, London. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 276 pages, $55.00.

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: June 8-12, 1984, Valdez Convention Center.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: 1985—date and place to be announced.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and Country, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 20-22, 1984, Mark Marriott, Vail.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: November 9-11, 1984, Kauai Surf Hotel, Kauai.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-28, 1984, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1985—date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1985—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: 1985—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 24-28, 1984, Jackson Lake Lodge, Moran.

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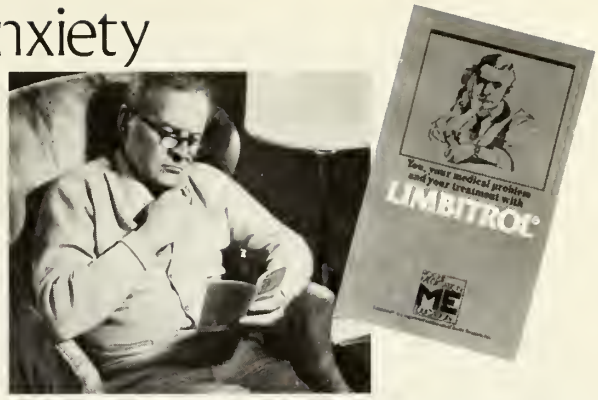
*Feighner JP: *Psychopharmacology* 61 217-225, Mar 22, 1979.



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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose* packages of 100, Prescription Paks of 50.

ROCHE®
ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

CLEARING: BOTH THE DEPRESSION AND THE ANXIETY...

ROCHE

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

Please see summary of product information on reverse side.

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